“PREVALENCE AND PREDICTORS OF RENAL ARTERY STENOSIS (RAS) IN CORONARY ARTERY DISEASE (CAD) PATIENTS UNDERGOING CORONARY ANGIOGRAM (CAG)"

DISSERTATION SUBMITTED FOR

THE FULFILLMENT OF

DOCTOR OF MEDICINE

BRANCH I – GENERAL MEDICINE

APRIL 2013

GOVERNMENT STANLEY MEDICAL COLLEGE & HOSPITAL

THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

CERTIFICATE

This is to certify that this dissertation entitled **"Prevalence and predictors of Renal artery stenosis (RAS) in coronary artery disease (CAD) patients undergoing Coronary angiogram (CAG) in Government Stanley Hospital, Chennai"** submitted by **DR.AROCKIAA PHILO AARTHY.J** to The Tamil Nadu Dr. MGR Medical University is in partial fulfillment of the requirement of the award of M.D. DEGREE (BRANCH-I) and is a bonafide research work carried out by him under direct supervision and guidance.

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DECLARATION

I solemnly declare that the dissertation entitled **"Prevalence and predictors of Renal artery stenosis (RAS) in coronary artery disease (CAD) patients undergoing Coronary angiogram (CAG) in Government Stanley Hospital, Chennai"** was done by me at Government Stanley Medical College and Hospital during 2012 under the guidance and supervision of **PROF.** and **HOD of GENERAL MEDICINE, Dr.S.MAGESHKUMAR M.D.** The dissertation is submitted to the Tamil Nadu Dr.MGR Medical University towards the partial fulfillment of requirements for the award of M.D. DEGREE (BRANCH –I) in General Medicine.

Place :

Date : **Dr. J.Arockiaa Philo Aarth**y

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Prevalence and predictors of Renal artery stenosis (RAS) in coronary artery

BY AROCKIA PHILO AARTHI 20101053 M.D. GENERAL MEDICINE

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CONTENTS

INTRODUCTION

The true prevalence of atherosclerotic renal artery stenosis (ARAS) is higher than the number reported because of the lack of specific clinical symptoms and signs and lack of appropriate guidelines for evaluation of ARAS. Early identification of ARAS helps in preventing the renal and cardiovascular morbidity and mortality.

There is sparse available Indian literature about the occurrence of ARAS in CAD individuals. This study intends to study the percentage and predictors of ARAS in CAD individuals undergoing CAG in Government Stanley Hospital, Chennai. Identifying clinical risk factors would enable stratifying patients and identifying those patients in whom screening renal angiography would be indicated.

REVIEW OF LITERATURE

Renovascular disease is the occlusion of renal arteries or of one of its branches by atherosclerotic, fibromuscular, or inflammatory lesions, which may lead to renovascular hypertension, pulmonary edema or renal failure, referred to as ischaemic nephropathy. [2]

NORMAL ANATOMY

The kidneys are located against the posterior abdominal wall against T12- L3 vertebrae. The kidneys are retroperitoneal organs. It is bean shaped. The hilum on the medial border is the site where the renal artery, renal vein and the ureter are located. It has the renal lymphatics and nerves also. At the superior border is the adrenal gland.

Each kidney is enveloped by the following coverings: The inner renal capsule, the middle adipose capsule and the outer renal fascia.

A coronal section of the kidney show kidneys, the outer renal cortex, adjacent to the renal capsule, which is granular in appearance and composed of capillaries and the inner medulla made of conical pyramids. The apices of the renal pyramids are called as renal papillae. The collecting system of the kidney consists of the minor calyx, major calyx followed by the ureter.

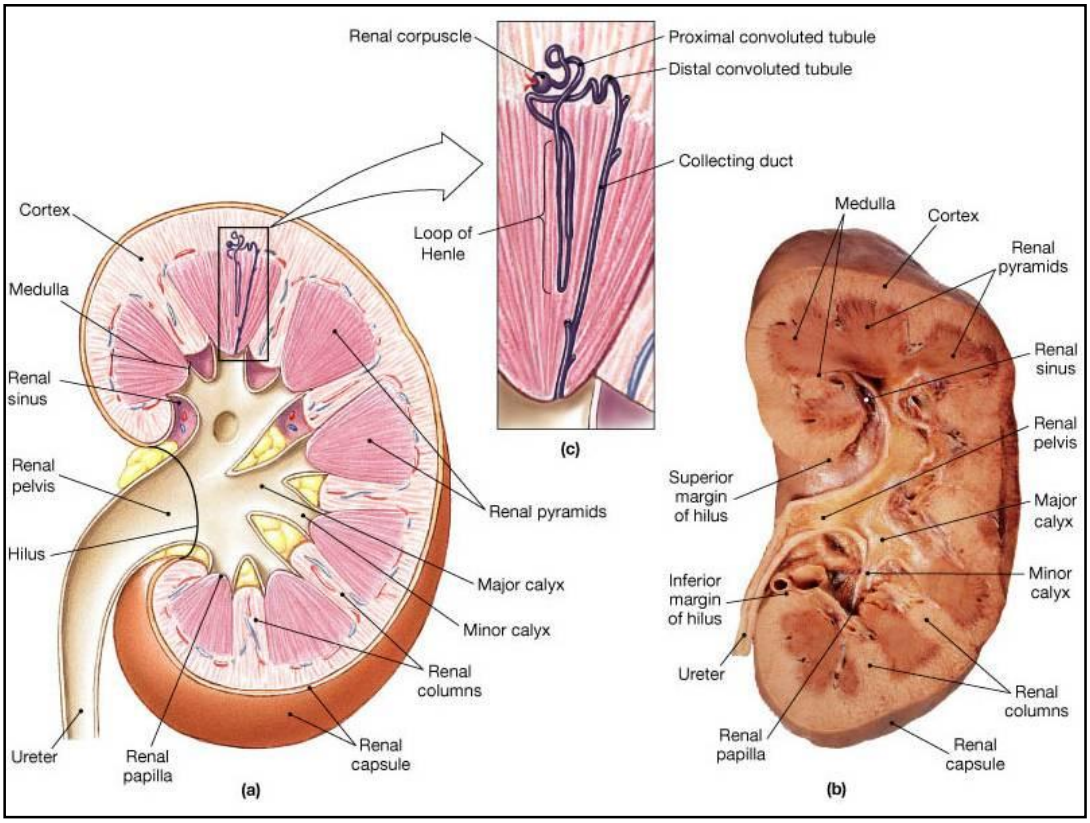


Figure 1: Anatomy of the kidney. (a) & (b): Gross anatomy of the kidney, (c): Structure of a nephron

The nephron is the structural and functional unit of the kidney that performs the function of filtration and concentration of urine prior to excretion. The Gross anatomy of the kidney and the structure of a nephron are shown on Figure 1.

RENAL BLOOD VESSELS

The kidney is rich in vascular supply which allows continuous cleansing and modification of large volumes of blood. The descending aorta gives rise to the main renal artery.

The renal artery branches into interlobar arteries that lead into arcuate arteries that lead into interlobular arteries. Microscopic afferent glomerular arterioles arise from branches of the interlobular arteries. The afferent glomerular arterioles transport blood into the glomeruli.

The blood remaining in the glomerulus leaves after filtration passes through the efferent glomerular arterioles. From these capillary systems, blood drains into veins which parallel the course of the arteries in the kidney, namely the interlobular veins, arcuate veins, and interlobar veins. The interlobar veins run in between the renal pyramids, converge, and leave the kidney as the renal vein that drains into the inferior vena cava.

Each kidney is supplied by the corresponding renal artery but there can be anomalous accessory renal arteries in 20- 30% patients. In a resting adult, the kidneys receive 1 to 1.4 L of blood per minute, or just under 25% of the cardiac output.

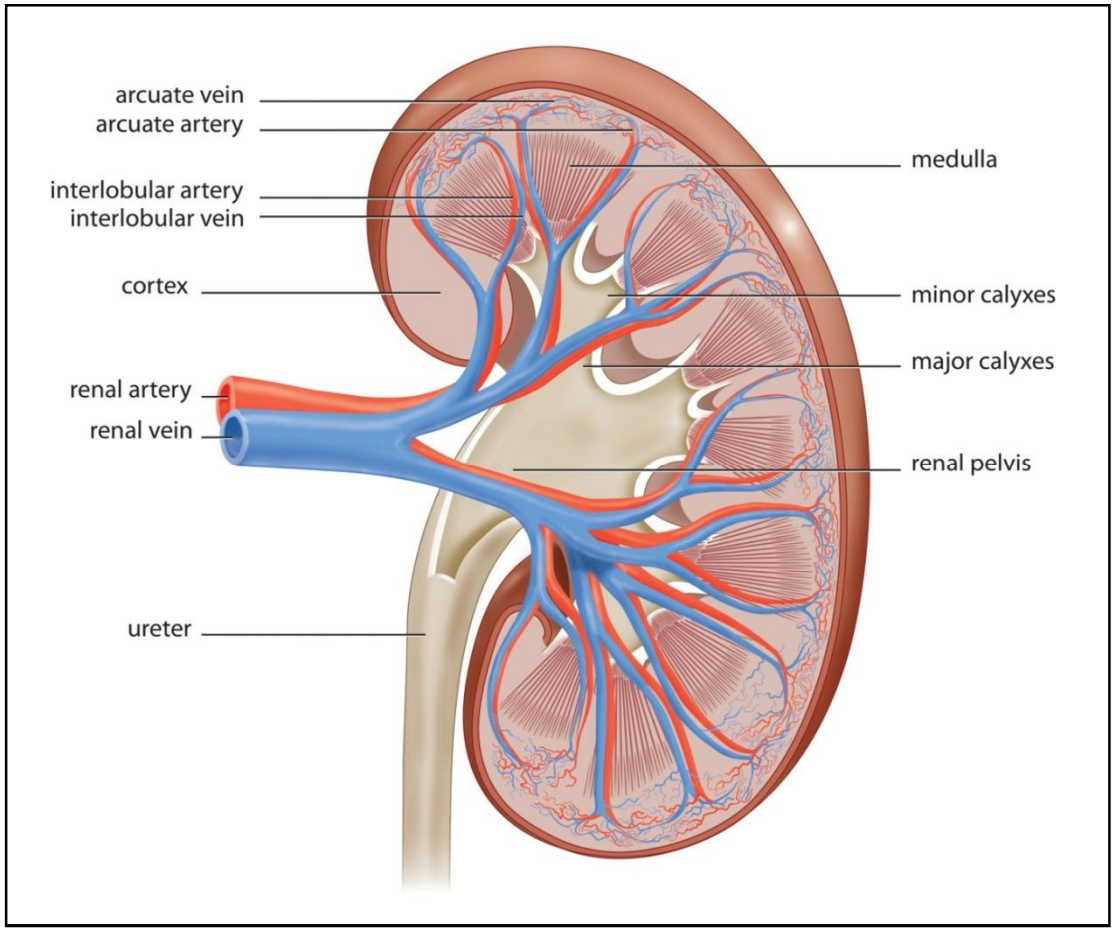


Figure 2: Renal Blood Vessels

Figure 2 shows the renal artery that enters at the renal hilum and its course in the renal cortex and medulla that eventually leads into the venous system which finally converge into the renal vein that exits at the hilum.

NORMAL PHYSIOLOGY

When the two kidneys normally function, their capacity of performing the function of excretion is twice of what the body requires to

maintain homeostasis. But with aging due to decrease in renal blood flow, the function deteriorates to 45% of normal by the age of 80 years.

Blood flow (Q) in a vessel is given by Darcy's law, $Q=\Delta P/R$, where ΔP is the pressure difference between the two wends of the vessel and R is the vascular resistance. [3] The vascular resistance increases when the flow is turbulent, by obstruction to the flow. Compensation to lumen stenosis happens upto a certain extent by increase in the flow velocity.

RENAL AUTOREGULATION

When the kidney is perfused at moderate pressures (90-220 mm Hg in the dog), the renal vascular resistance varies with the pressure and the renal blood flow is almost constant. It is proposed to be due to a direct contractile response of the afferent arteriolar smooth muscle to stretch mediate by Nitrous Oxide and angiotensin II.

PATHOPHYSIOLOGY OF ATHEROSCLEROTIC RENAL ARTERY STENOSIS (ARAS)

Renal artery stenosis (RAS) is an abnormal change in the vascular lumen which becomes hemodynamically significant when reduced >50%.[4] Critical RAS occurs when the renal arterial lumen is reduced by more than 60%. Critical stenosis refers to the degree of stenosis at which

flow and pressure begin to be reduced, any further increase in stenosis would significantly decrease the flow and pressure.

ETIOLOGY OF RAS

The most common cause of RAS is atherosclerosis followed by fibromuscular dysplasia. Critical (>60%) stenosis is observed in 9% men and 5.5% women over 65.[5] The occurrence is higher in those individuals with coronary (19%) or peripheral (35–50%) vascular disease.

PREVALENCE OF ATHEROMATOUS RENAL ARTERY STENOSIS[4]

i) 25% of autopsy samples

ii) 24% patients undergoing renal angiography during cardiac catheterisation

iii) 45- 50% patients having peripheral vascular disease

iv) 15% patients undergoing renal dialysis

ARAS occurs in the middle-aged and elderly, most commonly male smokers. Bilateral involvement is seen in 50% cases.

The aortic ostium is the most frequent anatomic location. It occurs because of the rapid blood flow through the renal artery due to the rich vascular supply and also the angulation at the renal artery origin.

Turbulent flow causes endothelial injury at this site, that predisposes to atherosclerosis at the site.[4]

BURDEN OF ARAS IN INDIA

Renal artery stenosis due to atherosclerosis is more frequent than those reported. Coronary artery disease is prevalent among 10% of urban Indian population and 8% of patients undergoing coronary angiography have significant ARAS.[6] Thus significant ARAS is estimated to be found in 0.8% of adult urban Indian population.[6]

The prevalence of ARAS causing advanced chronic kidney disease (CKD) or end stage renal disease (ESRD) is lower in India and found to be 0.3% of the CKD[6] and ESRD population. This shows that though highly prevalent, only few ARAS patients actually present as advanced CKD. This discordance could be because most ARAS patients may not progress to ESRD or they may succumb to the disease before they develop advanced CKD. Leertouwer et al reported that none out of 126 patients with ARAS survived over 10 years and Conlon et al reported that only one out of 188 over 4 years developed ESRD.[6]

In young women between 14- 52 years age, RAS occurs commonly due to an intrinsic structural alteration of the arterial wall due to

fibromuscular dysplasia, commonly seen to occur in the distal main renal artery.

Other uncommon causes of RAS are thromboembolic disease, vasculitis like Takayasu arteritis, Polyarteritis nodosa, post radiation, tumours like neurofibromatosis and lymphomas compressing the renal artery, retroperitoneal fibrosis or iatrogenic restenosis following angioplasty or other renovascular surgery. [7]

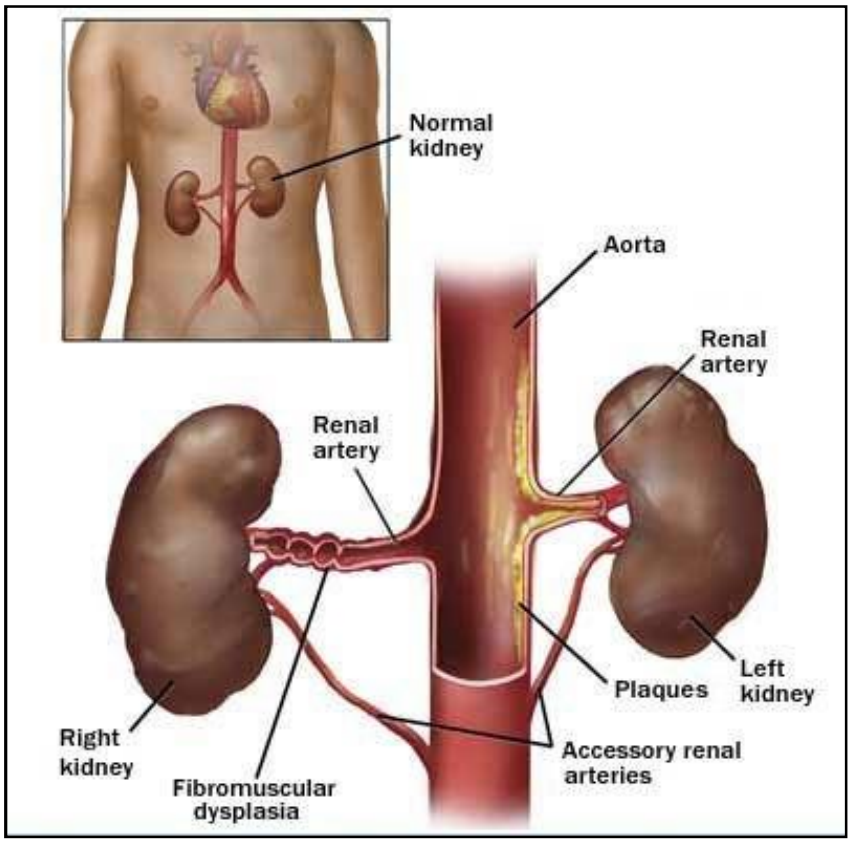


Figure 3: Common sites and etiology of Renal artery stenosis

NATURAL HISTORY

Atherosclerotic RAS is a generalised gradually progressive disease. High risk of progressive obstruction is observed in individuals with high systolic blood pressure, diabetes mellitus and those with pre-existing stenotic renal artery

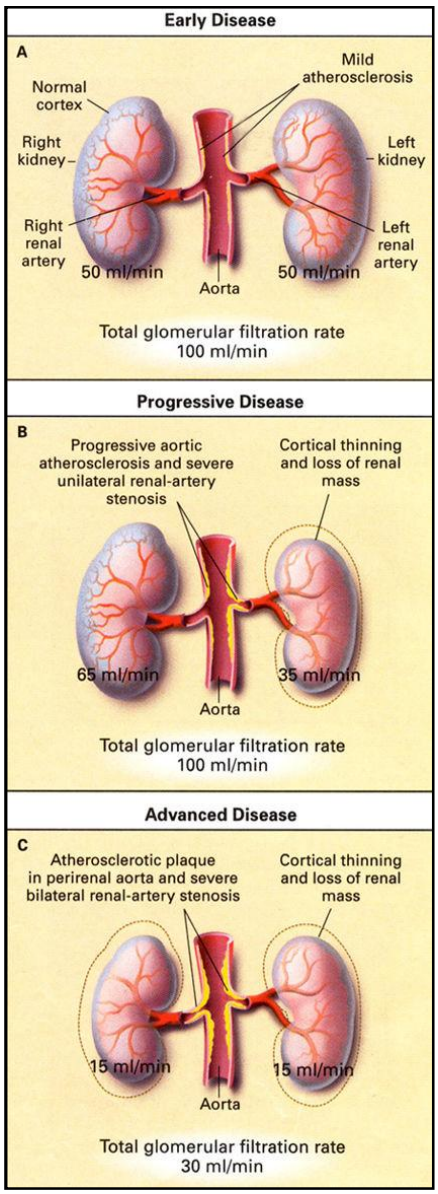


Figure4: Shows the progression of RAS and associated renal changes

PROGRESSION OF ARAS

Caps et al assessed the temporal profile of ARAS in 295 kidneys in 170 patients over 33 months.[8] Progressive vessel occlusion was measured to be a rise in the renal artery peak systolic velocity (RAPSV) of >0.1m/sec relative to the original value or complete renal artery obstruction. On a 3 year follow up, the incidence of renal artery stenosis in renal arteries found to be normal, less than 60% obstruction and >obstruction are 17%, 30% an 48% respectively.[8]

The group also analyzed the risk of renal atrophy (reduction in the length of the kidney by >1 cm). The cumulative incidence of renal atrophy was found to be significantly higher in ARAS >60% compared to normal or ARAS <60% initially. Multivariate regression analysis concluded that increase in RAPSV predicted renal atrophy, but not systolic blood pressure or renal cortical end diastolic velocity.[8]

Also serum creatinine in these patients who developed atrophy of both kidneys increased by a just 0.33 mg/dl/ year when compared to those who had no atrophy in both kidneys. These observations indicate that progression of ARAS is not necessarily associated with decline in GFR.

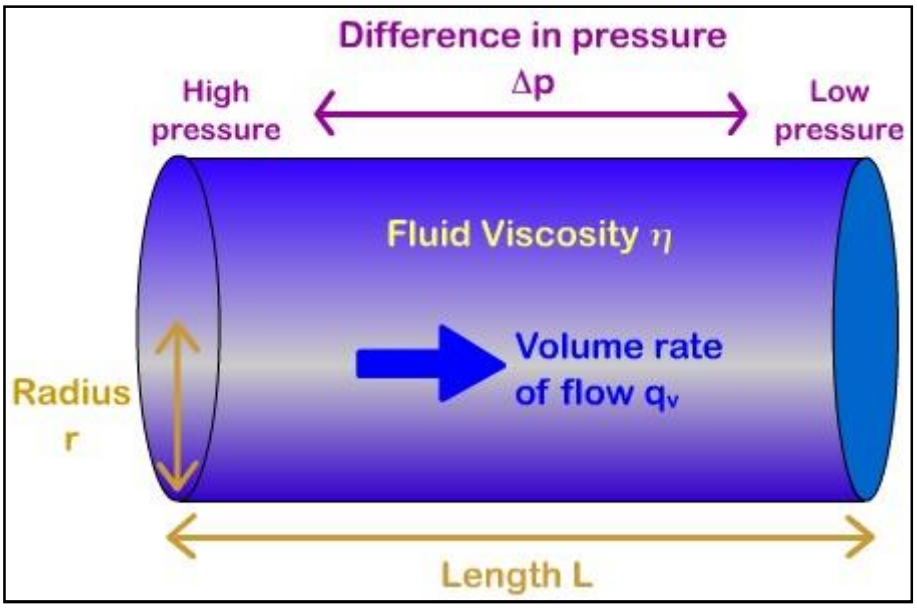
POISEUILLE' S EQUATION

For a steady laminar flow of homogenous fluid through a straight tube with rigid walls, blood flow(Q) is given by,

$$Q = \pi \Delta P r^4/(8L)$$

where ΔP= pressure gradient, r= radius of the tube, L= length of stenosis, = fluid viscosity.

Thus the primary factor determining the blood flow through a vessel is the diameter of the vessel. However the resistance in a blood vessel due to a stenosis is much higher than that predicted by Poiseuille's equation because the blood flow through a blood vessel is i) turbulent, ii) pulsatile and iii) blood is a nonhomogenous fluid with blood cells suspended in plasma.



HEMODYNAMIC EFFECTS DUE TO RAS

The hemodynamic changes in pressure and flow occur occur only beyond critical stenosis. The degree of stenosis which should occur to cause critical stenosis is determined by vascular resistance in the kidney, flow velocity, viscosity of blood and the number of stenotic sites in the vessel.

Once critical stenosis occurs the relation between the radius of stenosis and the pressure drop is exponential. Distal to the site of critical stenosis both blood pressure and flow are decreased in parallel. For RAS to cause renal hypertension and renal failure, the glomerular filtration pressure should fall.

The principal humoral and hemodynamic changes occurring due to RAS[4,10]:

1. Ischemia induced nephron loss
2. The stenotic kidney produces renin secretion
3. Angiotensin II induced vasoconstriction and hypertension
4. The renin secretion from the other kidney is reduced
5. Intrarenal vasoconstriction and so decreased renal blood flow
6. Aldosterone production is increased

7. Increased sodium and H_2O retention due to stimulation of the renin angiotensin system.

MECHANISMS CAUSING TISSUE INJURY IN ARAS

ARAS not only endangers renal function but also causes worsening of cardiac function. The pathogenetic mechanisms leading to these changes are being studied.

Atherosclerotic renovascular disease causing renal artery stenosis is not the only abnormality causing renal injury. There is no significant correlation between the amount of obstruction and the degree of renal injury.

Due to the renal artery stenosis there is hypoxia, oxidative stress, and a fall in renal perfusion pressure, dyslipidemia, increase in atherogenic factors in the circulation beyond the stenosis there is abnormal stimulation of the renal angiotensin aldosterone system that lead to the kidney injury observed.[9,13] Endothelial damage, decreased nitric oxide mediated vasodilation and large amounts of vasoconstricting substances cause large amount of free radical generation and oxidative stress.[9,10]

RAS AND VASCULAR ENDOTHELIAL GROWTH TO THE FACTOR (VEGF)

VEGF causes new blood vessel formation and for preserves the existing visceral blood vessels.[11,14] It plays a vital role in formation, reparative mechanisms and maintenance of the microvasculature of all organs including the kidney. VEGF prevents scar formation in the kidney.

The kidneys constitutively produce VEGF that acts on endothelial cells predominantly. Studies show that the reduced VEGF and so reduced microvascular density in RAS caused significant scarring of the renal tissue due to high renal vascular resistance, decreased renal blood flow and GFR.[11,12,15]

In the early stage of RAS, the local vascular supply i.e. blood supply/kidney tissue is preserved because of the fall in size of the kidneys and the microvasculature and renal blood flow. At a later stage, this compensatory mechanism does not act. Deleterious changes occur in the other kidney later stage contributing to the worsening of hypertension and subsequent renal damage.

Available literature shows that VEGF administration, increased the cortical and medullary microvascular density and significantly increased regional vascular supply and also helps to preserve the homeostasis of the

affected kidney. VEGF thus preserves pre-existing vessels and causes formation of fresh vessels.

CLINICAL PRESENTATION OF RAS

The salient clinical features of RAS are:

i) Renovascular hypertension

ii) Renocascular azotemia referred to as ischemic nephropathy

iii) Recurrent pulmonary edema

iv) Secondary hyperaldosteronism

i) RENOVASCULAR HYPERTENSION

It accounts for 1 to 5% of all hypertension cases[12]. The presentation is malignant or resistant hypertension commonly. Many patients with renovascular hypertension have hypertension not responsive to an appropriate regimen containing a combination of 3 drugs, in association with renal failure or with atherosclerosis at other vascular territories.

The mechanism of hypertension in ARAS is complex [9,12]. Animal studies show that a fall in the perfusion of the kidneys causes a series of events. There is synthesis of renin. Renin causes Angiotensin I from Angiotensinogen that is converted to Angiotensin II by Angiotensin I

converting enzyme. This angiotensinII deactivates kinins and thus promotes fall in blood pressure.

By directly causing vasoconstriction and hence hypertension, in addition angiotensin II increases total blood volume and thus promotes hypertension by its action on aldosterone and by promoting the vasoconstriction caused by norepinephrine.

The early phase of renovascular hypertension occurs due to activation of the the Renin Angiotensin aldosterone system and retention of sodium and water and expansion of extracellular fluid volume. In the chronic phase hypertension is volume dependent and renin release is suppressed.

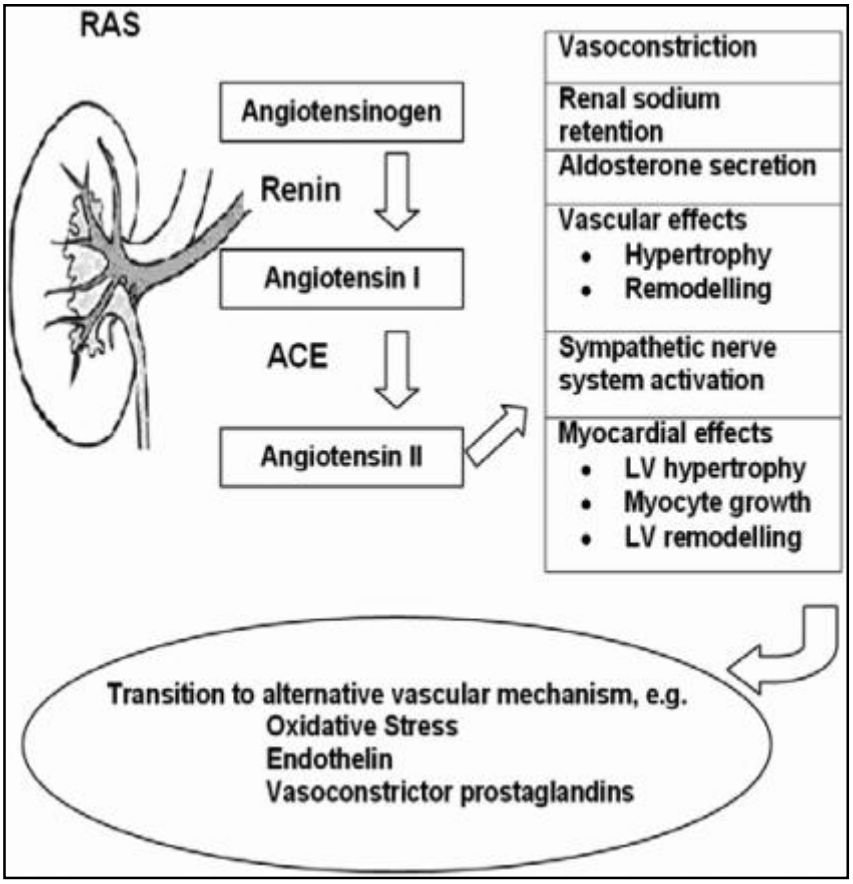


Figure 5:

Describes the the various mechanisms mediating renovascular hypertension. The complex mechanisms mediates changes in the kidney, the vascular system and the heart.

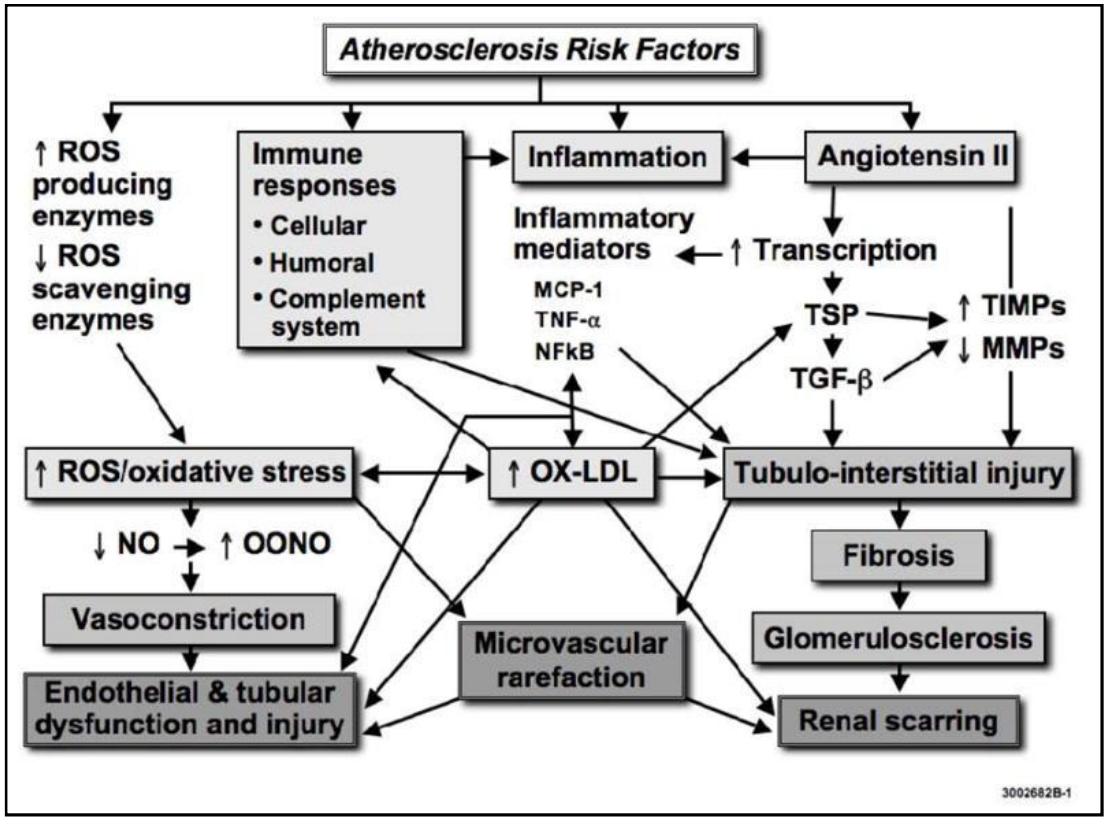


Figure 6:

Demonstrates the sequence of events occurring after acquiring atherosclerotic risk factors contributing to renal injury

Goldblatt's study describes 3 stages of renovascular hypertension in animal studies[10]:

i) **Stage 1:**

Sudden onset obstruction

ii) **Stage 2:**

Obstruction for a few days. Hypertension occurs and the plasma Renin and Angiotensin II levels rise, and clearing the occlusion causes the normotension and plasma Renin and Angiotensin II levels to normalise.

iii) **Stage 3:**

Obstruction lasts > 1 month. Plasma Renin and Angiotensin levels are normal. Removal of the obstruction does not cause the blood pressure to normalise.

Stage III reflects hypertension observed in patients with ARAS who are not strictly renin dependent[10]. ARAS sufferers with low renin and angiotensin II levels have a clinical improvement in blood pressure control after renal revascularization, but the beneficial outcome should be validated by future studies.

The Renin angiotensin aldosterone system mediated pressor effects and the increase in total blood volume mediated by stimulation of the sympathetic and central nervous system cause hypertension in ARAS.

Existing literature says that ARAS results in significant cardiovascular consequences significantly more than the severity of hypertension. Multiple mechanisms contribute to this. Angiotensin II is associated with numerous proinflammatory and damaging cardiovascular effects like myocardial fibrosis, arterial medial hypertrophy, endothelial cell dysfunction, smooth muscle cell proliferation, and plaque rupture.

Oxidative stress also seems to play a role in the hypoxic ischemic and hypertension mediated renal parenchymal injury in ARAS.

II) RENOCASCULAR AZOTEMIA REFERRED TO AS ISCHEMIC NEPHROPATHY:

RAS may cause acute kidney injury and chronic renal failure.

Acute kidney injury occurs in patients with vascular obstruction to a single functioning kidney or bilateral RAS taking medications blocking the renin angiotensin system. In most others it causes

glomerulosclerosis and chronic renal failure progressing to end stage renal disease. Most commonly causes a bland urine segment and non nephritic range proteinuria.

III) RECURRENT PULMONARY EDEMA

Recurrent acute onset flash pulmonary edema occurs due to retention of fluid and ventricular diastolic dysfunction.

IV) SECONDARY HYPERALDOSTERONISM

Associated with with low plasma sodium and potassium.

Clinical examination mostly reveals bruits over major vessels such as the abdominal aorta due to widespread atherosclerosis. The classical lateralising renal artery bruit is rare.

NEED TO SCREEN FOR ARAS

Early identification of RAS is important for the following reasons:

- Pharmacological management of RAS is difficult.
- High renin hypertension has higher rates of cardiovascular and cerebrovascular complications.

- Being a correctable cause of high blood pressure and terminal renal failure be identified and treated.

- Being a progressive disease and warrants early identification for better prognosis

Early identification of RAS can enable detailed evaluation of the renal artery anatomy, localisation of the lesion and timely intervention can help in avoiding complications and better prognosis.

ASSOCIATION OF ARAS and CAD

More than 50% ARAS patients develop ischemic heart disease or need cardiac revascularization procedures more frequently than non ARAS patients. The simultaneous occurrence of ARAS accelerates and worsens coronary artery disease and confers lower survival rates despite coronary revascularization.[16,17,18,19] ARAS does not have any specific symptomatology and there are no established guidelines for management of ARAS and hence it continues to remain unrecognized for a long time in the course of the disease.

Aetiopathogenesis of ARAS and CAD are similar and hence a significant association has been found between them.[17,18] Early attention to the kidney abnormality is associated with good blood pressure control,

normal renal function and a better outcome after coronary revascularisation procedures in CAD. The renal angiogram with angioplasty/stent can be done simultaneously using the equipment adapted for coronary angiography.

EVALUATION

ARAS is associated with advancing age, Chronic renal failure, smoking and other atherosclerotic risk factors. These characteristics may be associated with essential hypertension also.

The classic clinical clues that suggest the presence of ARAS are[5]:

- Onset of stage 2 hypertension > 50 years without any other family members having high blood pressure
- Together with renal failure (especially if renal failure increases after the use of renin angiotensin aldosterone system blockers)
- Recurrent flash pulmonary edema
- And drug-resistant hypertension

On clinical suspicion of ARAS, the diagnosis is confirmed by imaging as biochemical investigations such as plasma renin measurement confirmation are non specific.

SCREENING TESTS

DIAGNOSIS:

- Doppler Ultrasonography
- Magnetic Resonance Angiography (MRA)
- Helical Computed Tomographic Angiography (CTA)
- Renal Scintigraphy (using Captopril scan)
- Invasive Angiography
- Peripheral Renin levels
- Renal vein Renin sampling

Can be useful to identify ARAS.

Recommendations for screening patients for ARAS[20]:

1. Onset of>grade 2 hypertension >55 years age
2. Malignant or drug resistant hypertension
3. ACE inhibitor induced worsening renal function
4. Size difference of >1.5cm between the 2 kidneys
5. Recurrent sudden onset pulmonary edema
6. Multivessel coronary artery disease or peripheral vascular disease

CREATININE LEVELS AND GLOMERULAR FILTRATION RATE

It is a method of functional assessment and can quantitatively assess efficacy of renal interventions. Significant unilateral ARAS reduces GFR in that kidney but there is no alteration of the creatinine concentration until reduction of half of the overall kidney mass. Therefore the serum creatinine is not a reliable marker of the individual renal performance and renal mass[20]. It does not reflect the GFR totally. As the renal failure increases the creatinine correlates better with the GFR and with kidney performance.

GFR estimation by creatinine based formulae, MDRD or measuring GFR by iohexol clearance are relatively better indicators of renal function.

IMAGING STUDIES

An optimal imaging modality must meet the following 4 objectives[20,21]:

(1) ARAS must be identified and quantified based on severity anatomically and hemodynamically.

(2) Anatomic effects of ARAS both on the renal artery itself and on the kidney should be studied

(3) Effects of ARAS on the kidney at the functional and cellular level should be assessed (by captopril renography, the cellular viability of the renal parenchyma of chronic kidney disease patients is determined by diffusion-weighted magnetic resonance imaging

(4) Criteria associated with renal impairment related should be identified.

DUPLEX ULTRASONOGRAPHY

Duplex ultrasonography the most preferred initial imaging tool for the detection of RAS, although less accurate than CTA and MRA[20,22]. The advantages of preferring duplex ultrasonography is due to the absence of risks of contrast associated illnesses like contrast induced acute kidney injury, nephrogenic systemic fibrosis and atheroembolic disease[21,23].

However, undue reliance on the performer's skill, the inability to recognising accessory renal arteries and difficulty in screening obese patients or patients with intervening bowel gas are the limitations[20,23].

Ultrasonography provides information on kidney size, renal resistive index (RRI [defined as peak systolic velocity – end-diastolic velocity/peak systolic velocity]) and renal functional reserve. A high renal artery end-diastolic velocity (>90 cm/s) and low RRI (<75-80) indicate that there is no microvascular disease or increased resistance[24,25,26].

Widening of the spectrum and high velocity indicate that there is obstruction large enough to affect the vascular flow through the vessel[24,25,26].

The sensitivity and specificity of ultrasonography were 84% and 90%, respectively, in identifying hemodynamically significant ARAS according to a recent literature review. [20,22]

Severe stenoses causes tardus parvus alteration on the spectrum on Doppler ultrasonography, seen as a small systolic acceleration with a low resistive index[25,26,27].

Features suggested for the identification of distal stenoses are[20]:

i) Obliteration of early systolic peak acceleration (<3 m/s^2)

ii) Acceleration index greater than 4 m/s^2

iii) Increase in time to systolic peak greater than 0.07 seconds

iv) Greater than 5% difference in RRI between kidneys

COMPUTED TOMOGRAPHIC ANGIOGRAPHY (CTA)

ARAS usually occurs <1cm from the aortic wall. The luminal size of the renal artery is usually 0.4–0.6 cm. With three dimensional imaging CTA has become the ideal method for the identification of ARAS[28,29]. Because CTA radiation exposure and iodinated contrast agents, it is should not be used in patients with contrast allergy. Contrast-induced nephropathy associated with the use of iodinated contrast can be avoided by adequate hydration before infusing the contrast agent. For detection of ARAS the sensitivity of CTA is 95% and the specificity is 62% - 92%.[20,29,38,37]

In contrast to MRA, CTA identifies small accessory renal arteries due to its high spatial resolution. CTA is chosen over MRA in patients with various implants , patients who cannot hold their breath for long, and for patients with claustrophobia. However, specificity of CTA for detecting hemodynamically significant ARAS is less than that for MRA. CTA images of heavily calcified arteries are difficult to interpret .

MAGNETIC RESONANCE ANGIOGRAPHY(MRA)

Magnetic resonance angiography has a sensitivity and specificity of >90% .[30,31] It does not require iodinated contrast or radiation. Gadolinium-based contrast medium should not be used in patients renal failure due to potential to cause nephrogenic systemic fibrosis.

MRA should be avoided in patients with certain implanted devices or in patients with claustrophobic . MRA has no calcification artifact.[20,30,31,32]

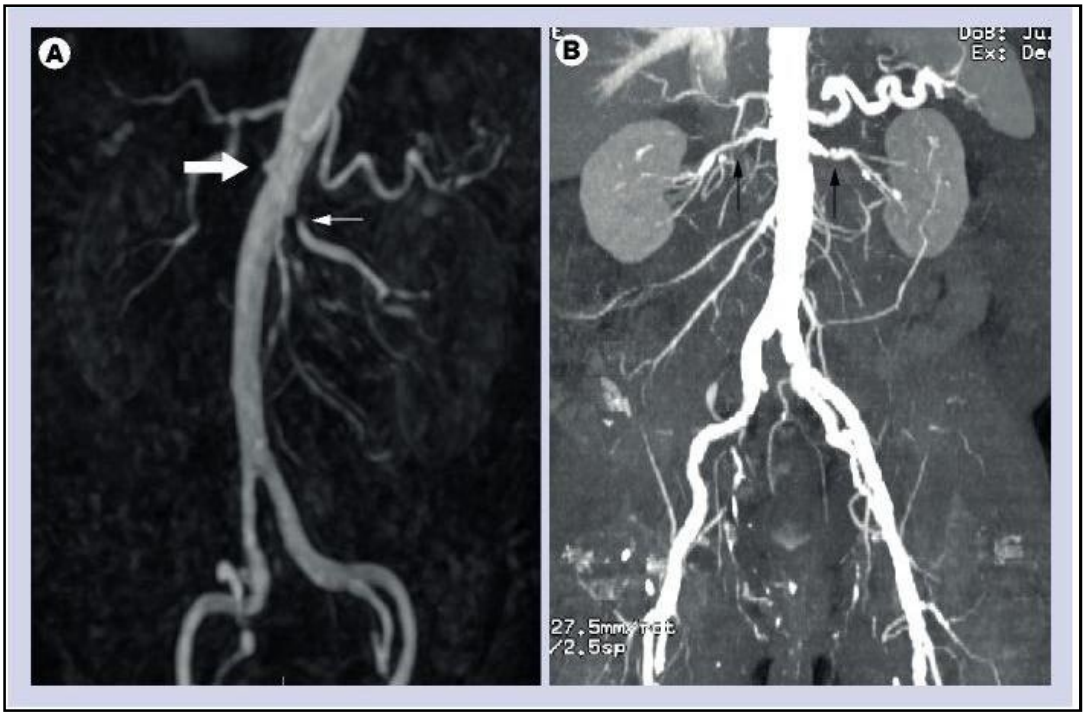


Figure 7:

Magnetic resonance and computed tomographic angiography of renal artery stenosis. (A) Demonstrates a magnetic resonance angiogram of severe bilateral renal artery disease. The right renal artery is occluded just after its ostium (white block arrow), and the left renal artery has a severe proximal stenosis (white arrow). (B) Demonstrates a processed reconstructed computed tomography angiogram of bilateral severe renal artery stenosis, marked with arrows to highlight the region of maximum stenosis.

CAPTOPRIL RENOGRAPHY

This functional test detects the GFR dependence of angiotensin II. If the test is positive by giving oral captopril of 25 to50 mg there is a delay in the uptake of tracer and there is a drop in the maximum peak uptake, prolongation of the duration captopril stays in parenchyma and slow removal, and also affects function of each kidney in unilateral disease.[20,31]

Its efficacy as a diagnostic tool drop in end stage renal failure, bilateral disease and if there is a single functioning kidney. It is preferred to predict the benefit from renal revascularization. But it is not advised for routine assessment of RAS .

ANGIOGRAPHY

Angiography can assess the degree of ARAS, and also detect vascular abnormalities and anatomic abnormalities of the kidneys and also the aorta.[20,32,34] Digital subtraction angiography has the advantage of improving contrast resolution and also requires less amount of contrast. But it is an invasive procedure, and has the risks of vascular puncture and manipulation of the vessel, that could lead to arterial trauma, spasm, or thromboembolic phenomenon. Carbon dioxide can be utilized in patients with kidney dysfunction or contrast allergy.

White et al study has proven that there is the possibility of significant observer differences in the estimation of degree of stenoses in coronary artery disease manually, that could also apply to the measurement of ARAS. Thus, to rely completely on angiography to quantify ARAS is not ideal, and additional methods should be used together to determine if there is renal injury.[32,35,36,38]

The pressure difference across the area of stenosis could be estimated angiographically to estimate hemodynamic effects prior to therapeutic interventions such as percutaneous transluminal renal angioplasty (PTRA) or stenting.[20,33,35]

De Bruyne et al found that obstruction with a distal to proximal renal artery pressure fall >10% caused more Renin secretion and thus proved that calculation of the pressure difference across the area of stenosis might help to study hemodynamically significant ARAS.[20,33,37]

MEDICAL THERAPY

Aggressive medical therapy can lead to improvement of ARAS patients. Use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers is advised for controlling hypertension and for improving outcome.[39] A drop in the kidney function after initiating these drugs is seen in bilateral RAS .

Timely administration of statins for optimal lipid levels, maintaining optimal glucose levels, and stopping cigarette smoking are important. No validated study has studied the effects of drug therapy on the management of renovascular hypertension as these patients often present as refractory hypertension and need combination therapy.[39]

Medications that block the renin-angiotensin-aldosterone system (RAAS) are preferred to manage high blood pressure in patients with ARAS, but they can predispose to acute kidney injury, in individuals severe bilateral ARAS, severe obstruction of a single existing kidney or if the other kidney is atrophied, or end stage chronic renal failure due to a fall in the perfusion pressure. Serial monitoring of the renal function is important as acute impairment in renal function due to these medications can frequently be reversed by prompt discontinuation of the offending agent.

Some studies have proved that individuals with high RRI (>80) benefit better with drug therapy than revascularization; however, using the RRI as the only indicator of medical therapy is debatable.[39,40]

Calcium channel blockers maintain renal blood flow by decreasing the tone of afferent arterioles and beta blockers lower renin.

Patient prognosis is good when agents that block the Renin Angiotensin Aldosterone system is used for treatment. Simultaneous use of diuretic agents should be avoided. The drug should be discontinued the serum creatinine rises more than 20% and interventional vascular therapy should be planned.

If both kidneys are involved or there is obstruction to a single kidney, ACE inhibitors should be used with caution, as renal failure can occur due to the dilation of the efferent arterioles that causes the capillary pressure in the glomerulus to fall less than the minimum required value and acute kidney injury can result <2 weeks after use of these drugs.

RENAL ARTERY REVASCULARIZATION

Successful percutaneous revascularization have not always given clinical benefit. Therefore if therapeutic revascularisation is indicated in ARAS and hypertension is debatable.

American Heart Association definition of significant RAS is as follows[20,40,42]:

(1) Occlusion of 50% - 70% lumen size by direct visual estimation with a peak translesional pressure difference > 20 mm Hg or a mean pressure difference of >10 mm Hg

(2) Occlusion 70% of vessel diameter

(3) Stenosis >75% diameter by ultrasonography done through the renal artery

But as per the recent American Heart Association recommendations, revascularisation should be done only for ARAS complicated by associated comorbidities.

Table 1: Shows the American Heart Association indications for Revascularisation of ARAS in the following scenarios: Asymptomatic stenosis, hypertension, renal failure and cardiac failure.

Asymptomatic stenosis
Percutaneous revascularization can be considered for treatment of an asymptomatic bilateral or solitary viable kidney with hemodynamically significant ARAS (class IIb, level of evidence [LOE] C)
Usefulness of percutaneous revascularization of asymptomatic unilateral hemodynamically significant ARAS in a viable kidney is not well established and is currently clinically unproved (class IIb, LOE C)
Hypertension
Percutaneous revascularization is reasonable for patients with hemodynamically significant ARAS and accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with unexplained unilateral small kidney, and hypertension with intolerance to drug treatment (class IIa, LOE B)
Preservation of renal function
Percutaneous revascularization is reasonable for patients with ARAS and progressive chronic kidney disease with bilateral ARAS or ARAS of a solitary functioning kidney (class IIa, LOE B)
Percutaneous revascularization can be considered for patients with ARAS and chronic renal insufficiency with unilateral ARAS (class IIb, LOE C)
Effect of ARAS on congestive heart failure and unstable angina
Percutaneous revascularization is indicated for patients with hemodynamically significant ARAS and recurrent, unexplained congestive heart failure or sudden, unexplained pulmonary edema (class I, LOE B)
Percutaneous revascularization is reasonable for patients with hemodynamically significant ARAS and unstable angina (class IIa, LOE B)

When interventional vascular therapy is contemplated , the severity of underlying nephropathy should be determined. ARAS with end stage renal disease do not significantly improve after revascularization.

The predictors of advanced nephropathy are:

1) Protein loss greater than 1000m g/d)
2) Kidney size < 10 cm
3) RRI > 0.8
4) Kidney biopsy demonstrating advanced nephropathy

The serum creatinine level is not a suitable marker of nephropathy.

PERCUTANEOUS TRANSLUMINAL RENAL ANGIOPLASTY (PTRA) FOR ARAS

INDICATIONS

Management of hypertension

a. A high possibility of cure of renovascular hypertension
    i. Onset of high blood pressure<30 years
    ii. Recent occurrence of high blood pressure > 60 years
    iii. Obstruction due to fibromuscular dysplasia
b. Blood pressure control is not responding to use of >3 drugs of different classes at optimal doses including a diuretic

c. Accelerated hypertension

d. Malignant hypertension with end organ damage such as cardiac failure, neurological effects, III–IV retinopathy.

Protection of kidneys

a. Renal failure that cannot be accounted
b. Decrease in renal size while treating hypertension
c. Renal dysfunction on taking antihypertensive drugs
d. Gradual extension of ARAS

Cardiovascular disease

a. Sudden severe pulmonary edema as a consequence to heart failure
b. Unstable angina

Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study is the largest randomized trial that compared medical therapy and PTRA of about 100 patients randomly assigned to angioplasty and drugs. If the disease was not responding to medical therapy they were subjected to PTRA.[20,41,43]

Major limitations of DRASTIC study

1) Registration of patients with less than significant stenosis
2) 40% were shifted from medical therapy to angioplasty
3) Very small stent usage about 25%

Patients in the angioplasty group did not significantly improve in terms of blood pressure or renal artery size in 1 year follow up.

RENAL ARTERY STENTING

Renal artery stenting has better success and less restenosis than angioplasty and also higher cure rates for hypertension. Renal stent use is safe and better than other measures to achieve blood pressure control.[44,46]

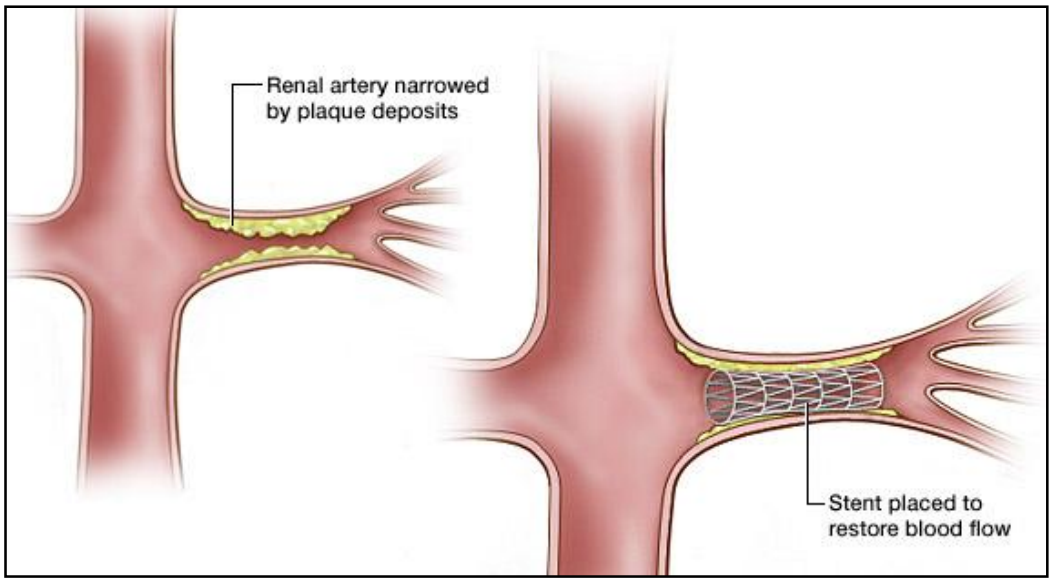


Figure 8 : Renal artery atherosclerotic plaque (left image) and Renal artery stent in situ to restore blood flow (right image)

There are 2 studies comparing renal artery stenting with medical therapy.

The Stent Placement in Patients with Atherosclerotic Renal Artery Stenosis and Impaired Renal Function (STAR) trial studied around 150 patients with a creatinine clearance of <80 mL/min/m, RAS >50%, and good blood pressure control was randomized to renal artery stenting together with drug therapy or only drug therapy.[45,47]

The expected outcome is a >20% fall in GFR, and the other end points were better overall prognosis. It proved that stenting with drug therapy caused no significant improvement in renal function but caused life threatensing complications.

Limitations of the study

1) Patients without ARAS were wrongly identified as having ARAS >50% by screening tests and there was no need for stenting, but were intentionally treated in the stent group
2) 33% study participants had only minimal RAS between 50% and 70% and greater than 50% patients had involvement of a single kidney. Because the primary end point was an improvement in functional performance of the kidney, these patients did not benefit much from interventional vascular therapy.

The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial studied 806 subjects with ARAS subjected to renal revascularization plus drug therapy or only drug therapy. The primary outcome evaluated was the performance of the kidney and secondary outcomes were blood pressure control, time taken for complications to occur. The patients were followed up for nearly 3 years. No significant clinical benefit from revascularization was observed in patients with ARAS but the associated risks proved significant.[46,47,48]

Limitations of the study

i) Study participation was limited to patients who were on an

ii) Uncertain treatment protocol and this led to strategy selection bias .

iii) 20% of patients had normal kidney performance, many patients had involvement of a single kidney and about 40% had a mild to moderate stenosis. It was concluded that the negative results were largely due to the high registration of patients with involvement of a single kidney who would benefit much from revascularization.

iv) No suitable apt investigations and imaging studies enables accurate and unbiased recognition.

In the follow up period >50% of centers enrolled less than a patient in a whole year, due to significant adverse effects incidence. The findings of this trial indicate that use of renal stents offers no significant advantage for patients with RAS but cause significant risks.

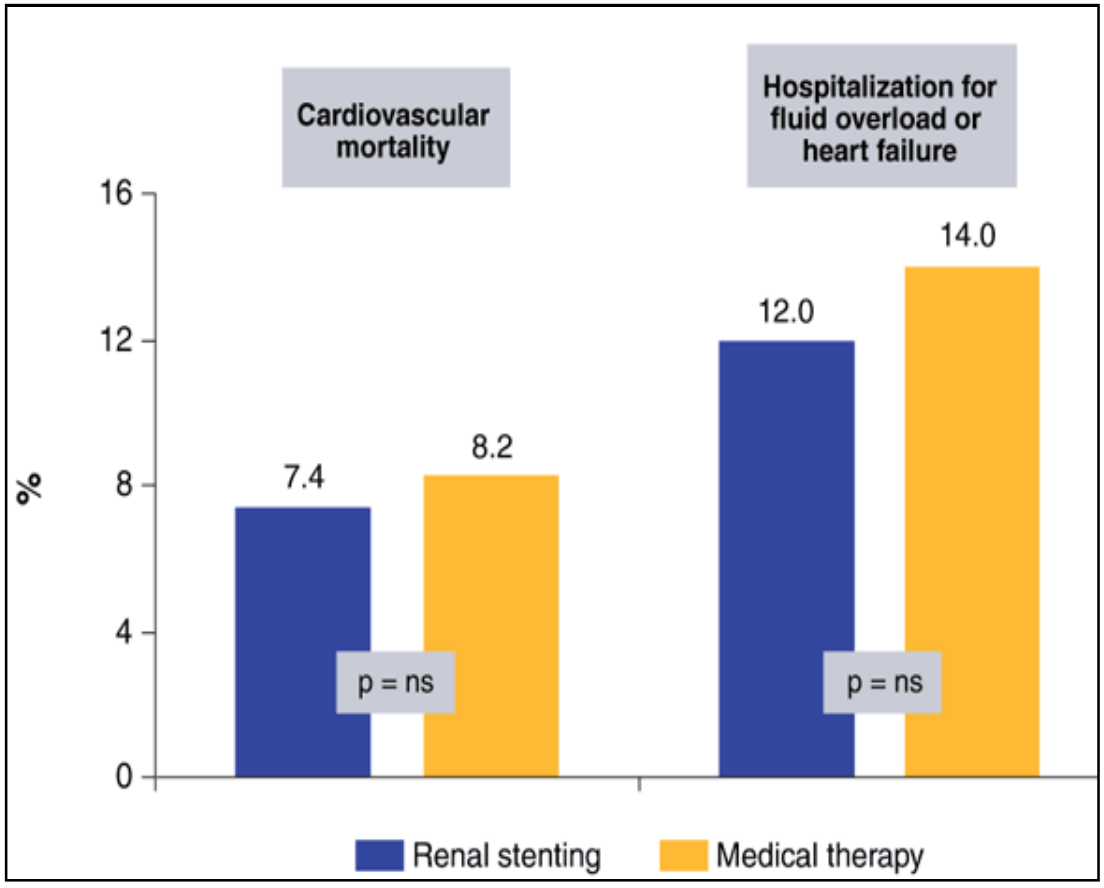


Figure 9: ASTRAL Trial results comparing medical therapy and renal artery stenting

The CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) study tries to analyze the benefits of PTRA with stenting together with drug therapy to medical therapy based on comparing complications.[47,48]

The study observed that prior trials lacked timely optimal drug therapy and lifestyle changes that could have halted the development of cardiovascular and renal ailments in this population. Therefore, CORAL trial emphasises on :

- Strict control of blood pressure by medications
- Avoidance of smoking
- Optimalisation lipid and glucose levels by appropriate therapy
- Administration of an antiplatelet agent

The clinical benefits of these interventions has not been established by population studies.

OTHER INTERVENTIONS

Brachytherapy and cutting balloon atherotomy can be tried for renal artery in-stent restenosis. The clinical benefits of these measures are unclear.[20]

Drug delivery stents used for coronary vessels can also be used for small renal arteries.[20] The optimal drug dose of the delivered drug for this vessel is not established.

The biggest drug eluting stent made is <0.4cm in diameter, that is of a smaller size than the renal artery (normal diameter of 0.5 to 0.7 cm).

Distal embolic protection devices can also br tried for removing atherosclerotic debris to stop it from distal embolisation. This helps to keep the renal function normal.

SURGERY

The results of surgical revascularization for ARAS have been good. But they are associated with significant morbidity and mortality relative to stent placement.

Very few literature sources are available for the comparison of surgical and percutaneous revascularization for management. In the Balzer et al study, no the long term outcome of the 2 modes of vascularisation proved to be similar[20]. But patients managed by surgery had a more reliable outcome. In terms of blood pressure regulation both were similar. The results of the study reveal that surgical

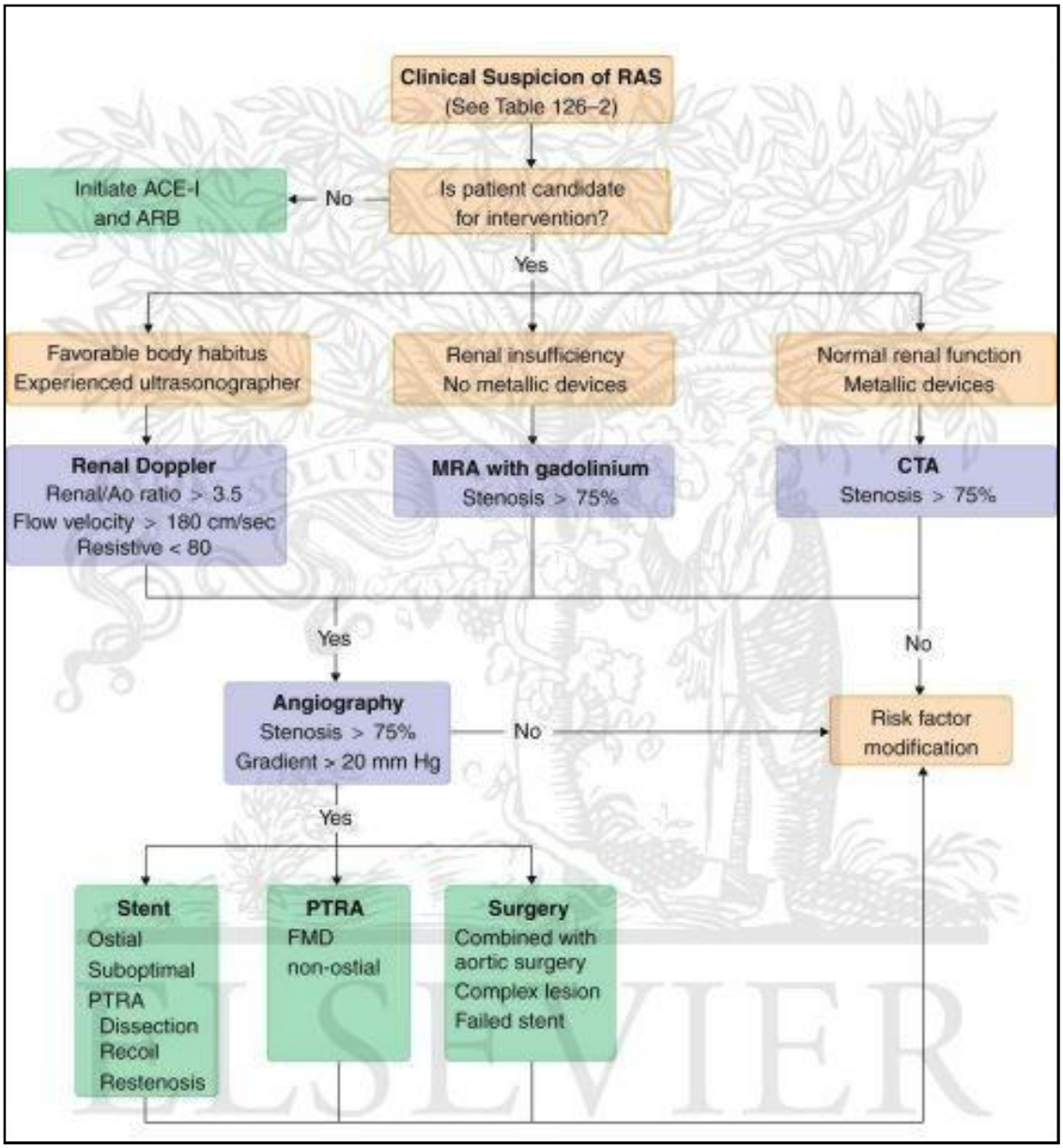
revascularization may be atleast equally effective as to PTRA for ostial ARAS.

Thus all patients with ARAS should be adequately managed medically. Early identification and timely medical treatment of ARAS avoids further cardiovascular complications. The benefits of revascularization are unclear.

Revascularization is indicated only in special situations like unstable angina, unexplained recurrent pulmonary edema, and hemodynamically significant ARAS associated with renal failure or resistant hypertension. Revascularization therapy has a vital role in the management of ARAS, but studies indicate that its use should be restricted to patients with renal ischemia with viable kidney function because only these patients receive the greatest clinical outcome.

FIGURE 10: MANAGEMENT PROTOCOL FOR RENAL ARTERY STENOSIS

DIAGNOSIS AND TREATMENT



CORONARY ANGIOGRAPHY

It is the gold standard investigation of choice for confirming and localizing coronary artery disease.

The American College of Cardiology (ACC) has prescribed clinical scenarios when Coronary angiogram should be done.

INDICATIONS FOR CORONARY ANGIOGRAPHY

CLASS I: General consensus is that there is an indication for Coronary angiography

CLASS II: Diverging opinions exist about the need for coronary angiography

CLASS III: Angiography should not be performed

Indications for Coronary Angiography

CLASS I:

- Acute coronary syndrome not responding to medical therapy
- Myocardial infarction with cardiogenic shock
- Myocardial infarction(MI) panned for Percutaneous coronary intervention (PCI)
- Continuing chest pain after fibrinolysis

- Abnormal stress exercise test after fibrinolysis
- Congestive cardiac failure with angina
- Abnormal chest pain<9 months of PCI
- Stress test is positive and patient has high-risk features
- Sudden cardiac death or ventricular arrhythmia without a predisposing illness
- Congestive cardiac failure with angina or ischemia
- Patient requiring valve surgery or repair of a congenital defect, with angina
- Suspected stent occlusion
- Before repair of a mechanical complication of MI
- Planned vascular surgery with angina or positive stress test

CLASS II:

- Acute Coronary Syndrome responding to medical therapy
- If reperfusion has not occurred after fibrinolysis after ST elevation MI
- Deteriorating ischemia after noninvasive testing
- Perioperative Myocardial infarction
- Positive stress test with no high-risk features
- Angina that is intolerant or unresponsive to medication
- Post cardiac transplantation every year for follow up

CLASS III:

- Patient does not prefer invasive vascular therapy
- Patient has medical comorbid illness not suitable for invasive vascular therapy
- Within 24 h of fibrinolysis with no evidence of ischemia
- Screening of asymptomatic patients

Scenarios when Coronary Angiography should not be done:

- Kidney dysfunction
- Bleeding Tendencies
- Any active bleeding source
- Fever or active infection
- Aortic valve vegetation
- Anemia
- Severe dye allergy
- Metabolic abnormalities
- Hyperkalemia
- Hypokalemia
- Digitalis toxicity
- Uncontrolled hypertension
- Decompensated heart failure

- Uncontrolled tachyarrhythmia
- Untreated high-grade heart block

The only absolute contraindication to coronary angiography is patient refusal.

PREPROCEDURAL MEDICATION

1) Aspirin, 325 mg administered to eligible patients before angiography if angioplasty is indicated.

2) If the probability of percutaneous intervention seems high, a loading dose of Clopidogrel, 300 mg, can also be given.

3) Metformin (Glucophage) should be discontinued on the day of the procedure, because this medication may cause lactic acidosis if renal failure results from the procedure and if metformin is continued after the onset of renal failure.

4) Warfarin should be stopped before the procedure if possible until the international normalized ratio is less than 1.8. If anticoagulation is essential, warfarin can be stopped several days before the anticipated procedure, and subcutaneous injections of the low-molecular-weight heparin, enoxaparin (1 mg/kg twice daily), can

be substituted; the dose of enoxaparin can then be withheld the morning of the procedure.

CONTRAST AGENTS USED

Iohexol, iopamidol, metrizamide, and ioversol are the nonionic, low-osmolal agents used today. Intravenous hydration with normal saline or 0.45% saline and maintenance of adequate hydration (100 mL fluid per hour or more) during and after the procedure reduce the risk of worsening renal function in patients with baseline renal insufficiency, particularly diabetic patients at risk of renal failure.

Concomitant nephrotoxins should not be administered. When renal failure occurs, it may not manifest for 24 to 48 hours. Hence, the creatinine measurement the morning after the procedure may be of limited value. The rise in creatinine may not occur until at least 24 hours after the procedure, peaking approximately 5 days after the procedure, and, commonly, resolving by the tenth day. However there is no occurrence of renal failure with use of nonionic contrast agents.

Acetylcysteine has been shown to reduce the occurrence of contrast nephropathy in small studies. It is important to limit the quantity of contrast agent used in patients with chronic renal insufficiency. Limiting

the quantity of dye to less than 30 mL markedly decreases the need for subsequent dialysis .

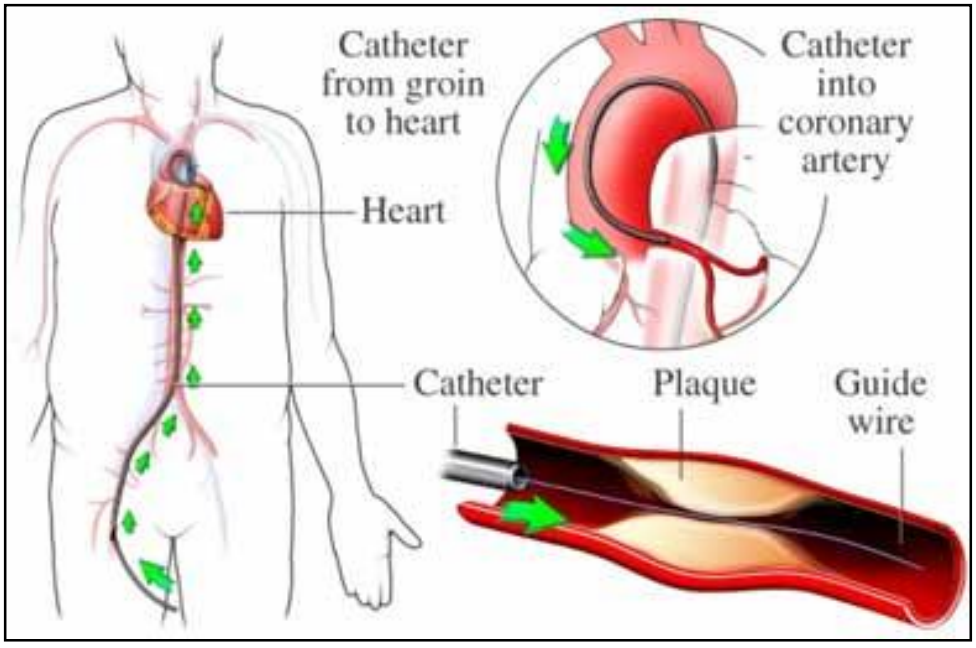
VASCULAR ACCESS

Performed through the Femoral Artery or the Radial Artery

FEMORAL ARTERY ACCESS

Most commonly used access route across the globe. Catheter manipulation is easier relative to the radial access.

Figure11: Demonstrates the route of access to the coronary arteries through the femoral artery



RADIAL ARTERY ACCESS

Advantages of this technique include easy compressibility and shorter times to ambulation. Before cannulation of the radial artery, it is advisable to perform an Allen test to ensure the adequacy of ulnar circulation to the hand. Another concern with radial artery cannulation is the possible need for this artery as a bypass graft conduit in the future.

COMPLICATIONS

Complications of angiography are very rare. The following complications have been reported occasionally.

1. Death
2. Myocardial ischemia
3. Cerebrovascular accident
4. Cardiac rhytm abnormalities
5. Contrast reactions
6. Cadiac perforation

AIMS AND OBJECTIVE

1) To determine the prevalence of significant RAS in patients with CAD

2) Correlation between severity of CAD and RAS

3) To determine the predictive factors associated with RAS. The predictive factors studied are age, gender, smoking, hypertension, diabetes mellitus, hypercholestrolemia, preprocedure serum creatinine and extent of CAD.

MATERIALS AND METHODS

SOURCE OF DATA

A sample of 100 CAD patients admitted for CAG in Government Stanley Hospital, Chennai during the period June 2012 to November 2012.

TYPE OF STUDY:

-Observational study

INCLUSION CRITERIA

1) Suspected CAD was by ECG, Echo or TMT criteria
2) Creatinine clearance>60ml/min(By Cockroft and Gault equation)
3) Renal size of more than 9 cm on sonogram

EXCLUSION CRITERIA

1) Known case of RAS
2) Presence of single kidney
3) Known case of Chronic kidney disease

METHOD OF DATA COLLECTION

CAD patients identified based on ECG, Echocardiography or TMT criteria admitted for CAG in Government Stanley Hospital during the period June 2012 to November 2012 were chosen for the study after obtaining informed from the patients.

Demographic factors of the patients such as age, gender, smoking habit, diabetes mellitus, hypertension, positive family history of CAD were documented. The patient was subjected to blood investigations such as hemoglobin, complete blood count, random blood sugar, blood urea, serum creatinine, serum electrolytes, lipid profile. Creatinine clearance in ml/min was calculated using the Cockroft and Gault formula,

Creainine clearance = (140-age) * (Wt in kg) * (0.85 if female) / (72 * Cr)

Ultrasonogram abdomen was performed to look for the size of the kidneys and the renal cortical echoes.

CAG was performed by the radial or femoral artery approach to look for the sites(s) and extent of obstruction in the coronary vessels. Simultaneously, a renal angiogram was performed during the procedure to look for the presence of RAS, site of lesion, extent and whether

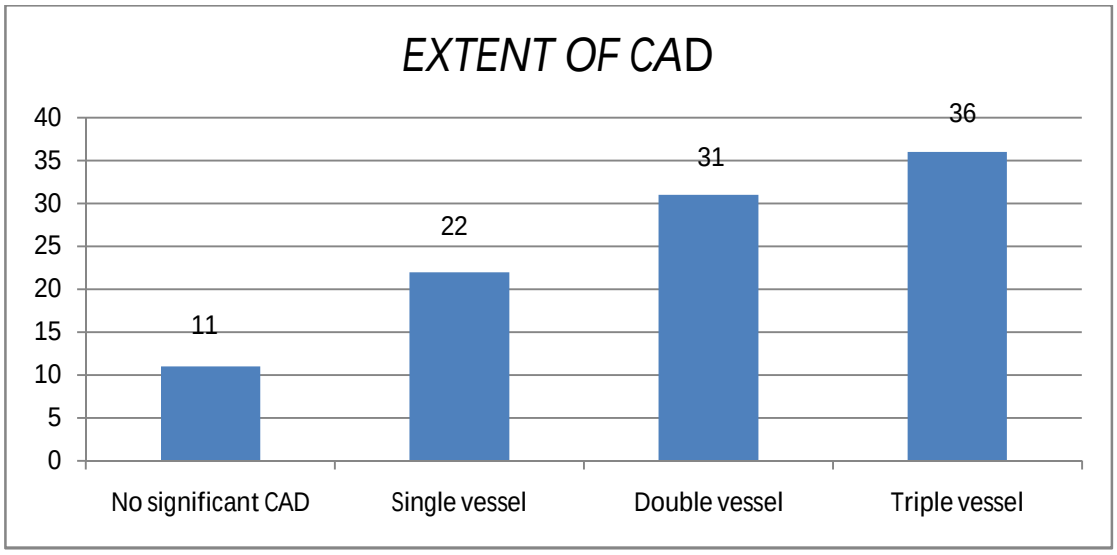
unilateral or bilateral. Multivariate logistic regression analysis was used to assess the relationship of the data.

RESULTS

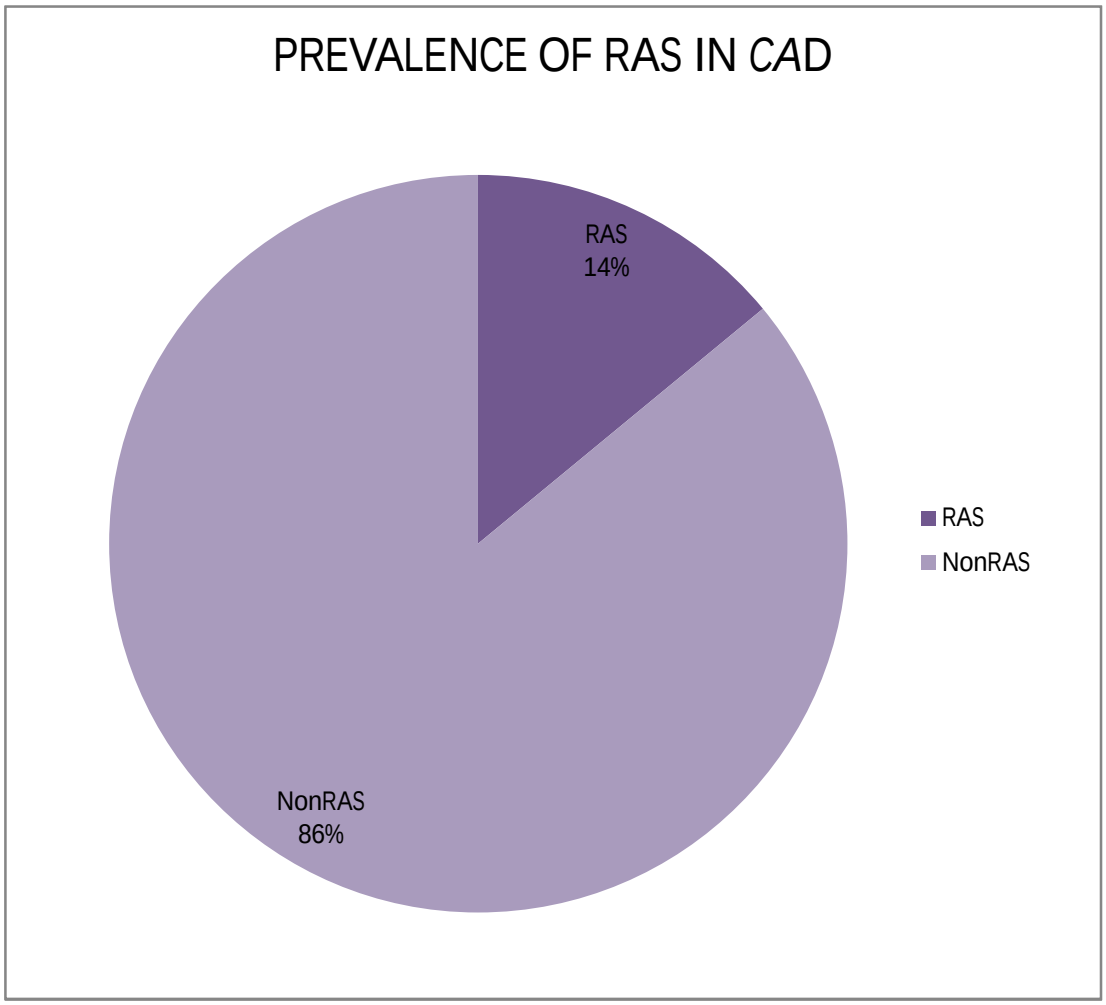
In the study, renal angiogram was done for100 CAD patients who underwent CAG, to look for the presence of atherosclerotic renal artery stenosis, the location and number of RAS sites involved.

Out of the 100 patients screened, 11 patients had no significant CAD, 22 patients had single vessel disease, 31 patients had double vessel disease and 36 patients had between triple vessel disease.

The patients in the study were aged between 42 and 70 years. 11 patients were aged between 42- 50 years, 55 patients 51- 60 years and 34 patients between 61- 70 years. In our study all patients found to have were above age 60 years.



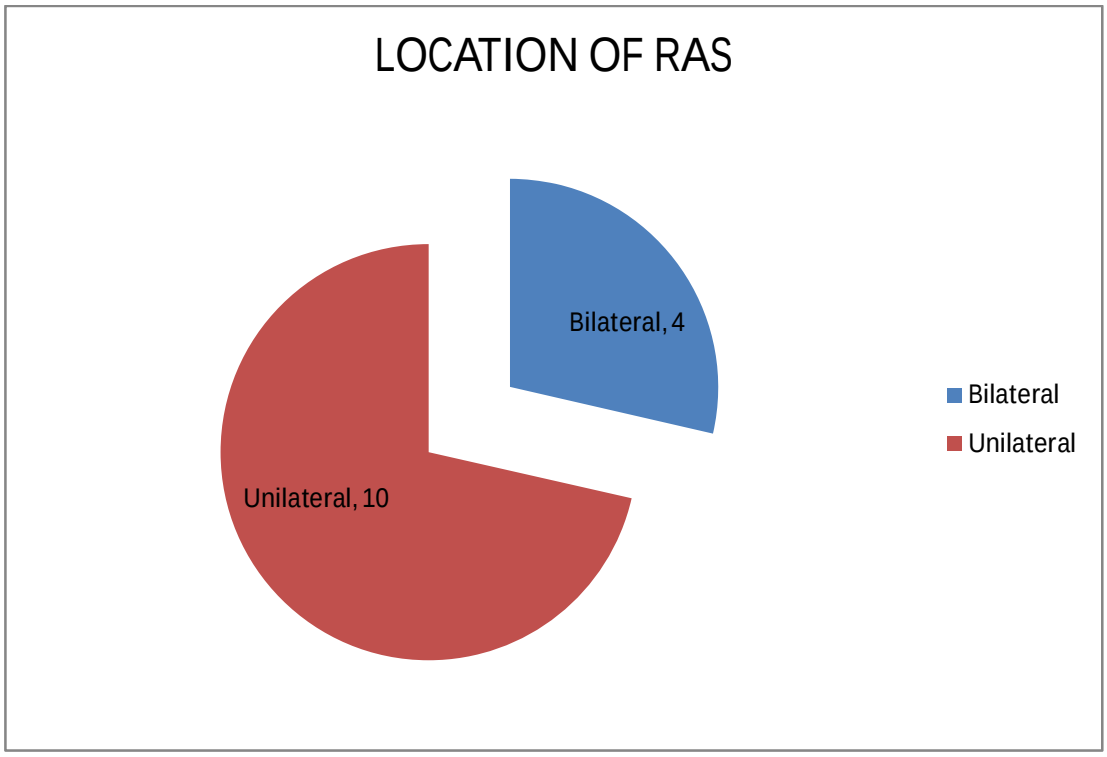
PREVALENCE OF RAS IN CAD



Out of the patients screened, 14 patients had significant renal artery stenosis, defined as a >50% obstruction of the renal artery lumen.

LOCATION OF RAS

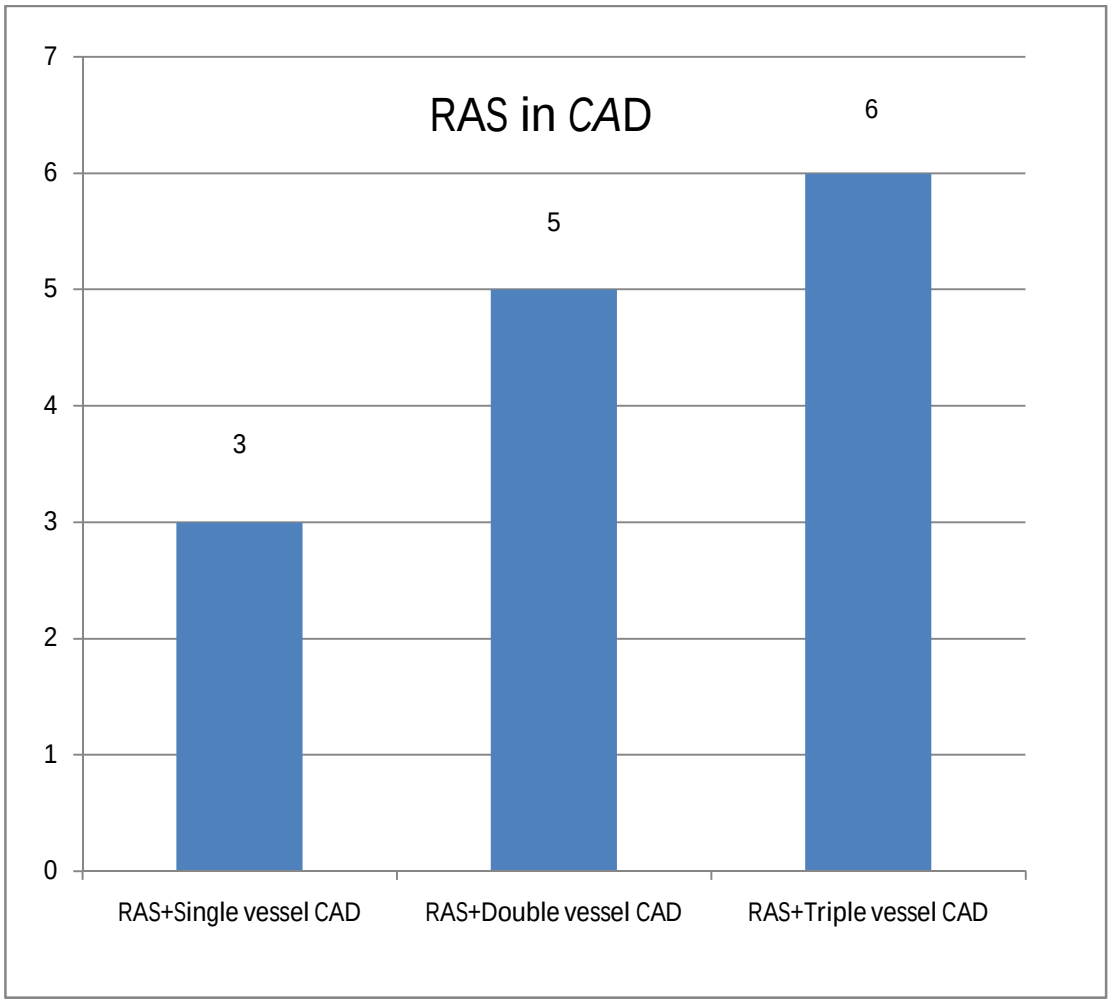
Out of the 14 patients with RAS, 4 patients had bilateral renal artery involvement while 10 patients had unilateral renal artery involvement.



It was observed in previous studies that RAS was more frequent in patients with multivessel disease which was reflected in our study also. 3 out of 14 patients had single vessel disease, 5 out of 11 patients had double vessel disease and 6 out of 11 patients had triple vessel disease.

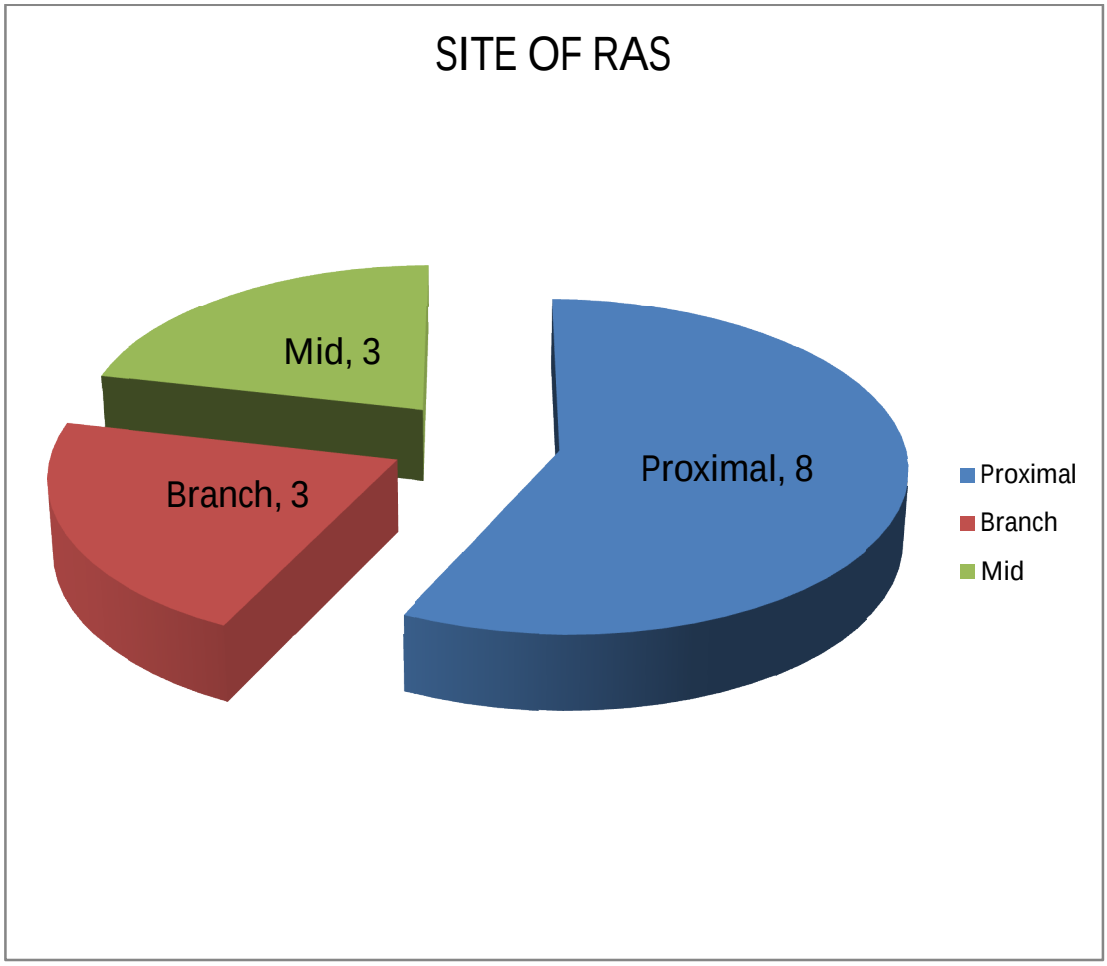
Using Pearson's chi-square test (p=0.007), we can conclude that the extent of CAD is significantly associated with RAS at 0.01 level of significance.

ASSOCIATION OF RAS AND EXTENT OF CAD



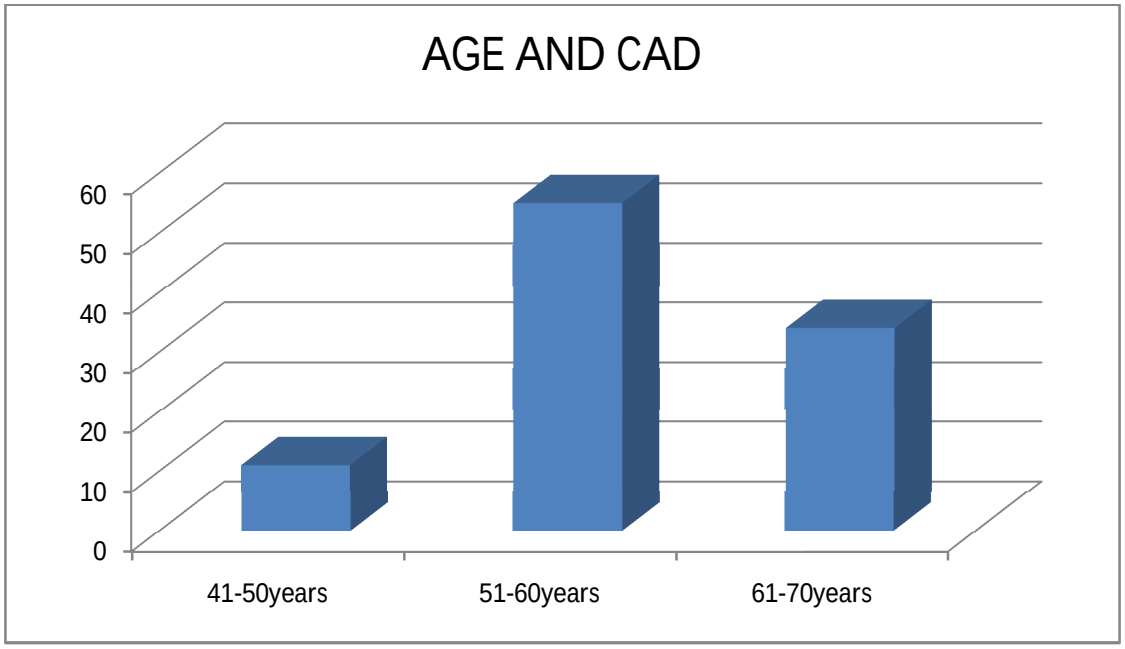
SITE OF RAS

Proximal renal artery stenosis has been previously observed to be the most common site of RAS. In our study too it was observed in 8 patients , and 3 patients had mid RAS and 3 patients had branch RAS.



AGE AND CAD

The patients in the study were aged between 42 and 70 years. 11 patients were aged between 42- 50 years, 55 patients 51- 60 years and 34 patients between 61- 70 years.

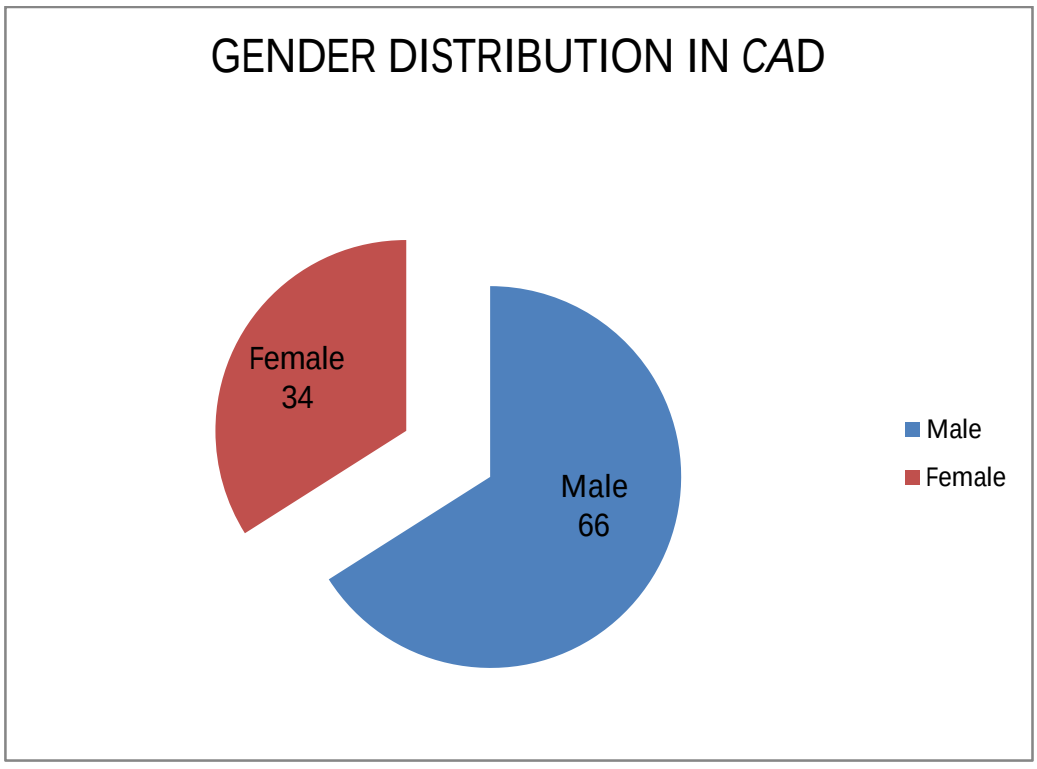


AGE AND RAS

In our study all patients found to have RAS were above age 60 years.

GENDER DISTRIBUTION OF CAD

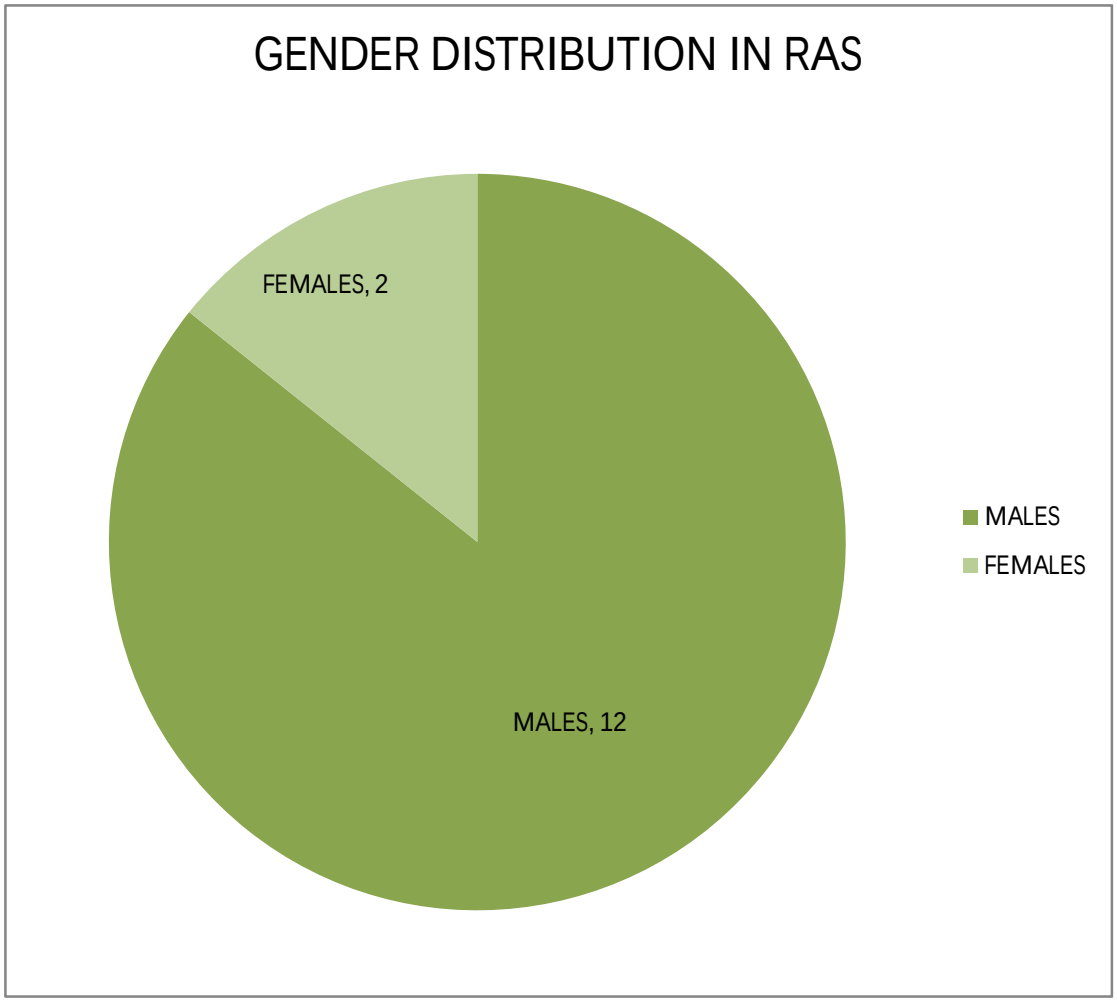
Out of the 100 CAD patients screened 34 patients were females and 66 were males. CAD is known to have a higher prevalence in male patients. Similar results were observed in our study.



Using Pearson's chi-square test (p=0.151), we can conclude that there is no significant association between gender and CAD at 0.01 level of significance.

GENDER DISTRIBUTION IN RAS

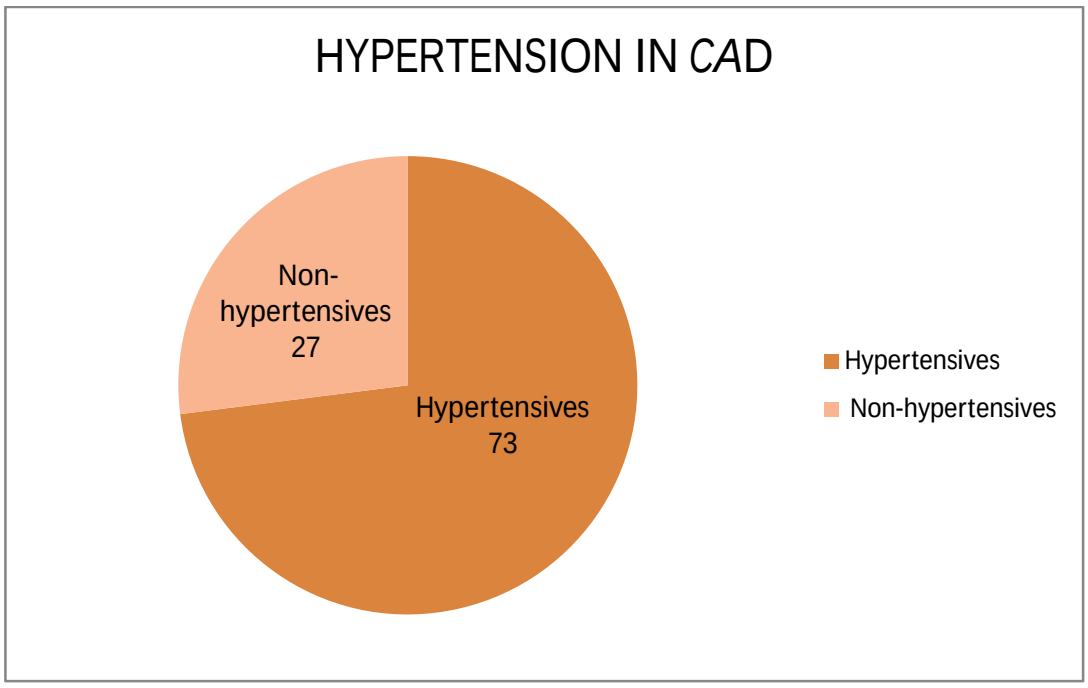
In our study RAS was much more common in males as compared to females. 12 out of 14 patients with RAS were males.



Using Pearson's chi-square test (p=0.103), we can conclude that there is no significant association between gender and RAS at 0.01 level of significance.

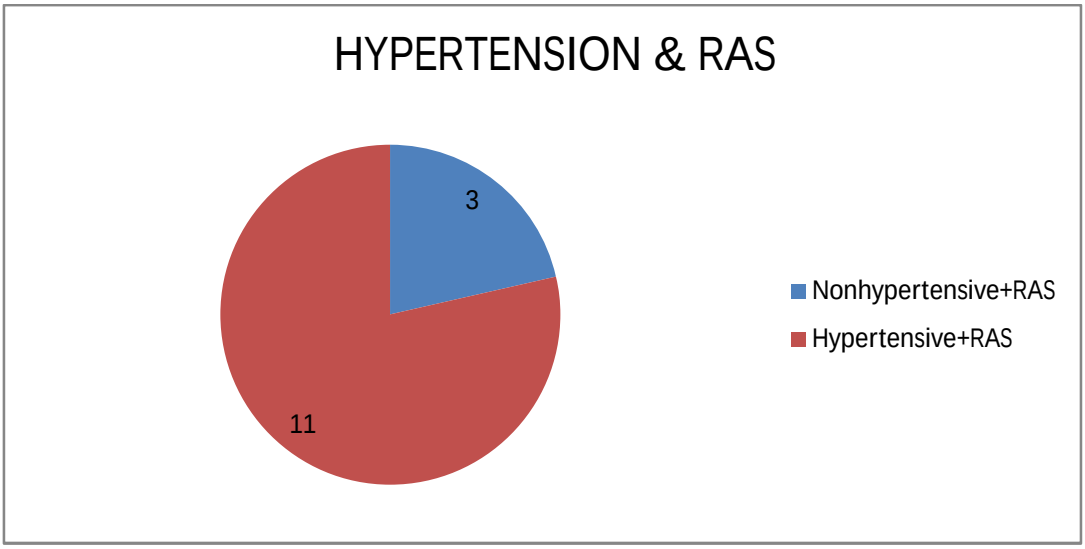
HYPERTENSION AND CAD

Hypertension is a known risk factor for CAD. 73 out of the 100 sample CAD patients were hypertensives.



HYPERTENSION & RAS

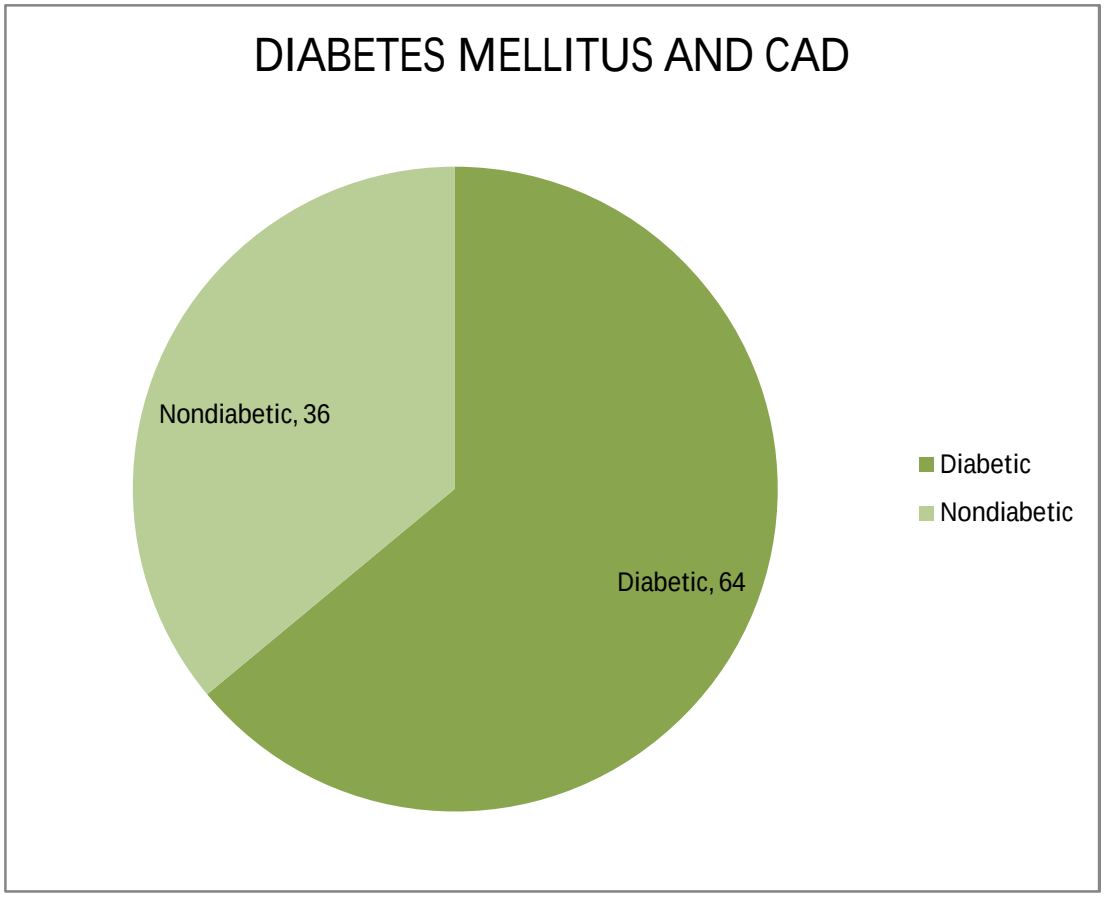
Like in CAD, RAS is more commonly seen in hypertensive patients . 11 out of the 14 RAS patients were hypertensives.



Using Pearson's chi-square test (p=0.657), we can conclude that there is no significant association between hypertension and RAS at 0.01 level of significance.

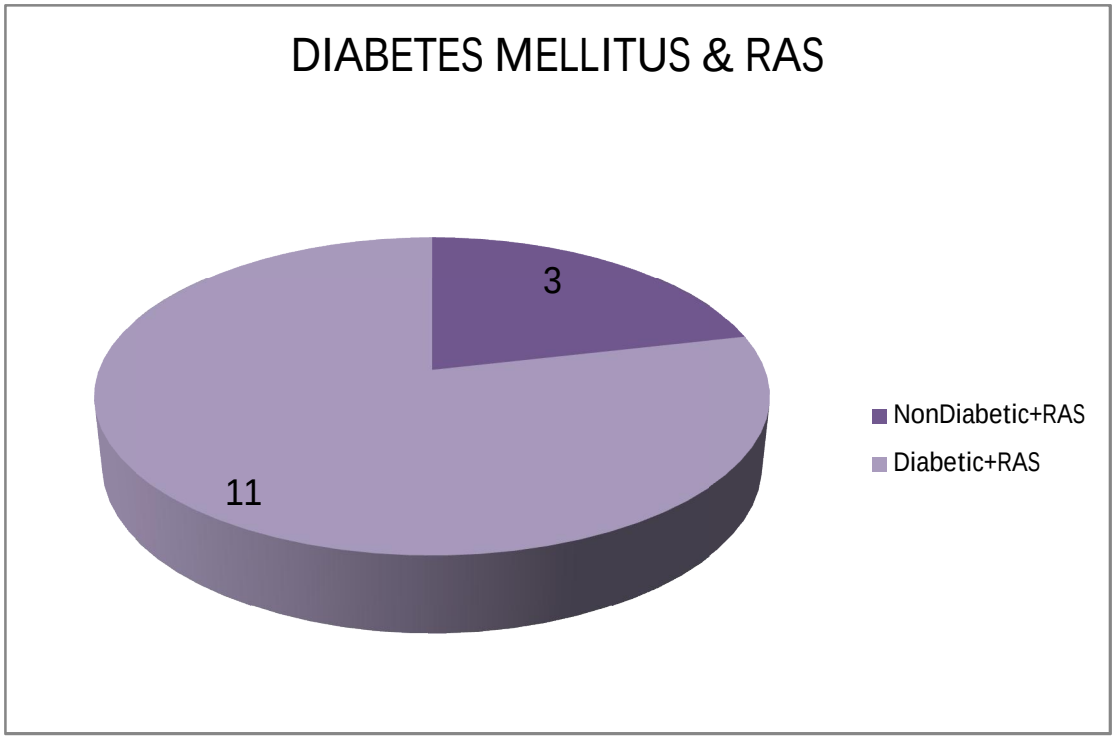
DIABETES MELLITUS AND CAD

Out of the 100 CAD patients studied, 64 patients were diabetic.



ASSOCIAION OF DIABETES MELLITUS AND RAS

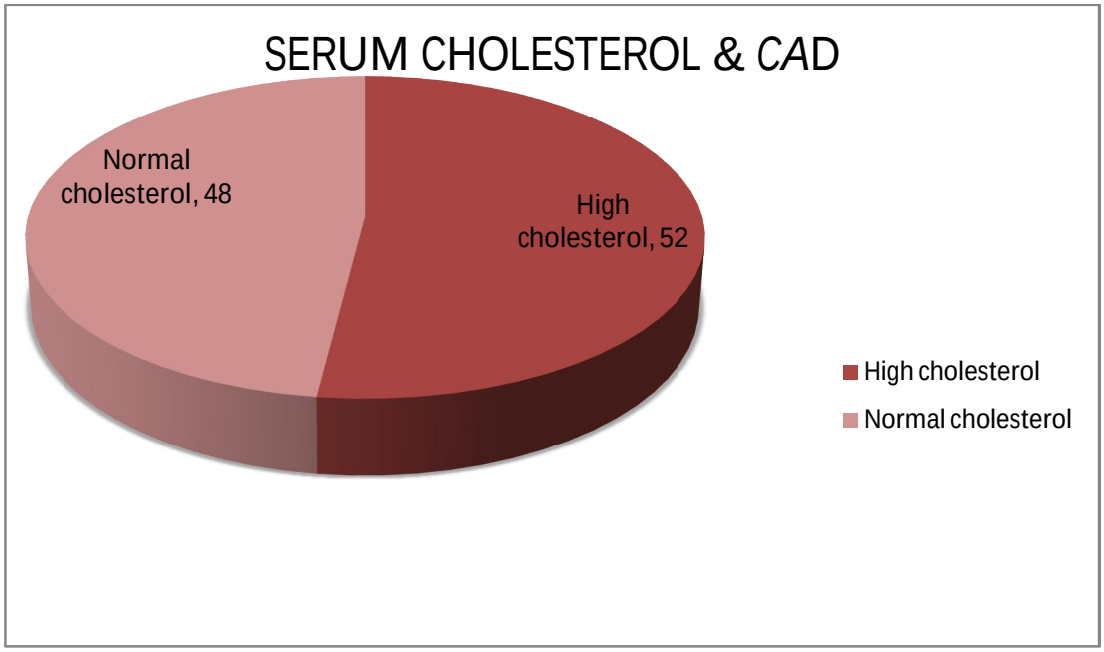
Out of the 14 RAS patients in our study, 11 were diabetic patients



Using Pearson's chi-square test (p=0.186), we can conclude that there is no significant association between diabetes and RAS at 0.01 level of significance.

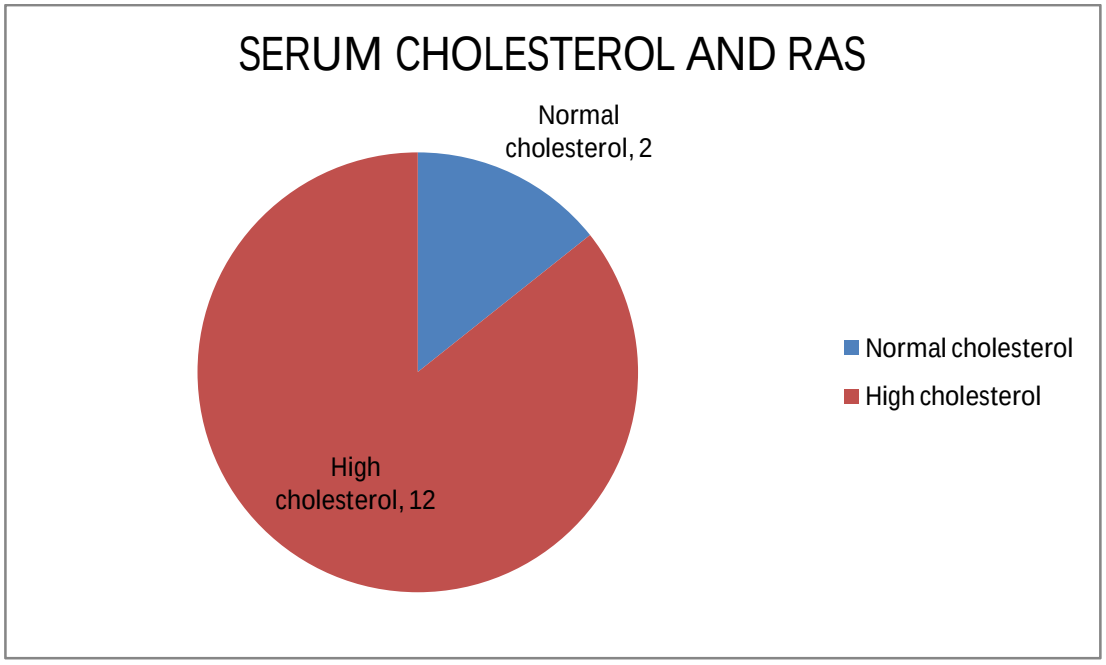
SERUM CHOLESTEROL AND RAS

The occurence of CAD was more prevalent among patients with hypercholesterolemia. Serum cholesterol cut off value was taken as 200mg%. 52 out of the 100 patients had high cholesterol levels.



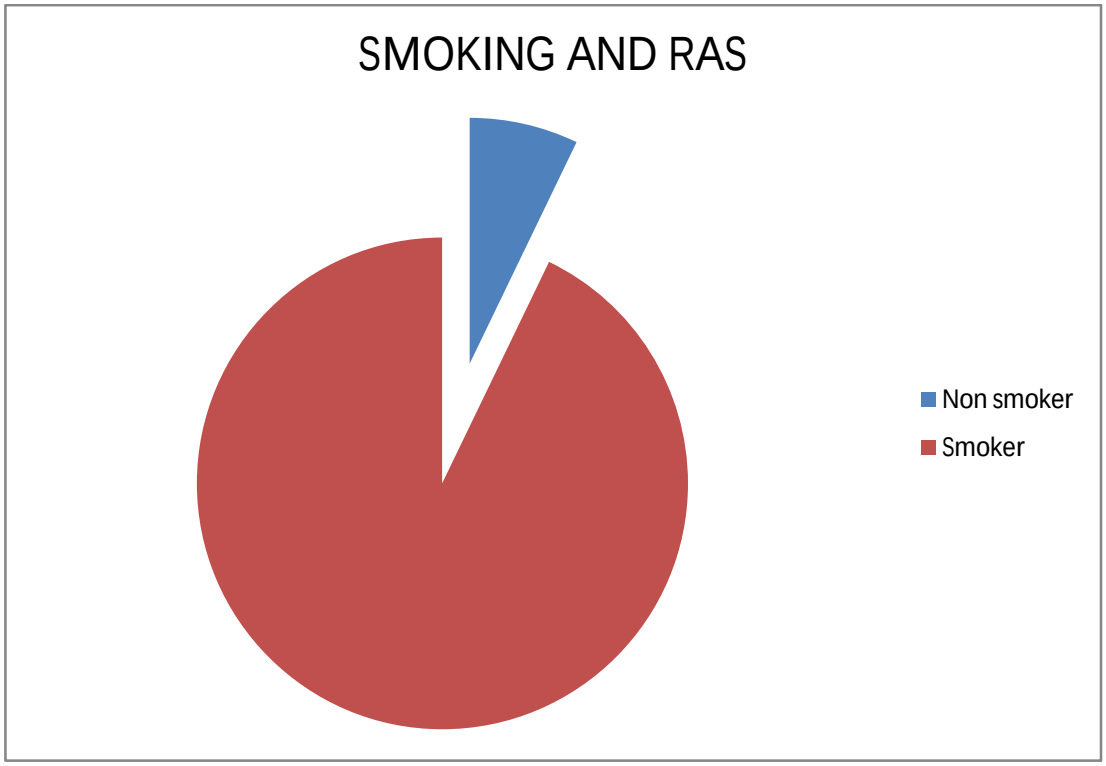
ASSOCIATION OF SERUM CHOLESTEROL AND RAS:

Out of the 14 RAS patients, 12 patients had high cholesterol levels while only 2 patients had normal cholesterol levels.



SMOKING AND CAD

68 out of the 100 CAD patients were smokers. Out of the RAS patients only 1 patient was a nonsmoker.



Using Pearson's chi-square test (p=0.035), we can conclude that there is no significant association between smoking and RAS at 0.01 level of significance.

MULTIVARIATE LOGISTIC REGRESSION

The following variables were found to be predictive at 0.01 level of significance:

Variable	Coefficient	Significance
Age	0.655	0.001
Serum Creatinine	21.371	0.005
Creatinine Clearance	0.354	0.001
Lipid Profile	6.022	0.002
Extent of CAD	3.927	0.008

Thus in our study, age> 60 years (p=0.001), creatinine clearance (p=0.001) lipid profile (p=0.002), serum creatinine (p=0.005) and extent of CAD were observed to be significantly associated with RAS at 0.01 level of significance.

Male gender, hypertension, diabetes mellitus, smoking were observed to be other independent risk factors.

The logistic regression was obtained to be:

Probability(patient having RAS)=

1/(1+exp(-(-102.247+(0.655*Age)+(21.371*Serum Creatinine) + (0.354*Creatinine Clearance)+(6.022*Lipid Profile)+(3.927*Extent Of CAD)+(4.327*Hypertension)).

It was observed that if probability (patient having RAS) > 0.5, patients were at a more risk of having RAS.

Using the above regression equation we were able to classify, 98% of non-RAS patients (84 out of 85) and 80% of RAS patients (11 out of 14) correctly.

DISCUSSION

Atherosclerotic renal artery stenosis (ARAS) is part of a common atherosclerotic phenomenon that occurs at multiple vascular sites in the body. It can lead to potential complications discussed above and hence early identification is important.

PREVALENCE OF ARAS

Our study demonstrates the total prevalence of RAS as 14% in a screening renal angiogram performed during coronary angiography. Cohen et al in 2005, screened the renal arteries in 843 patients who underwent cardiac catheterization and found the prevalence of RAS to be 12%.[49] In the Buller et al study done in 2001-2002, 851 patients were screened and renal atherosclerosis was observed in 332 patients.[50] In the Salehi et al study done in 2011, 500 patients were screened and the prevalence of RAS was found to be 25%. Other studies have also demonstrated the prevalence of RAS to be ranging from 10-20%.

LOCATION OF RAS

In our study the prevalence of unilateral RAS was 10% and that of bilateral RAS was 4%. In the Cohen et al study 84 patients had unilateral

disease and 15 had patients had bilateral disease.[49] In the Buller et al study severe bilateral stenosis was observed in 12 patients. [50]

Proximal renal artery stenosis has been previously observed to be the most common site of RAS and the same was observed in our study. 8 out of the 14 RAS patients had proximal renal artery involvement.

CAD AND RAS

It has been previously reported that the occurrence of RAS was found to be more frequent in multivessel CAD than single vessel disease. The same was seen in our study. 11 out of the 14 RAS patients had multivessel disease.

Previous studies have also reported the association of ARAS with atherosclerotic disease in vascular territories other than the coronaries including carotid artery disease and peripheral vascular disease. The association could be explained by the common pathophysiologic mechanism involving the renin angiotensin aldosterone system, altered lipid levels and excess oxidative stress accelerating atherosclerosis at various sites.

In our study multivessel CAD is associated with a p value of p=.008. In previous studies also it has been found that multivessel CAD

is an independent risk factor for RAS. In the Cohen et al study it has been found that the p value for association of RAS and multivessel disease is 0.40.[49] In the Buller et al study it has been concluded that the p value for the association of RAS and multivessel disease is 0.041.[50]

AGE AND RAS

Old age (>60 years) was significantly associated with RAS in our study population. Similar results have been obtained in previous studies. This may demonstrate a delayed onset of atherosclerotic disease in renal vessels. This has clinical implication as well. Screening renal angiography can be restricted to patients >60 years instead of performing them routinely in all patients.

GENDER PREVALENCE OF RAS

In most of the studies reported earlier, RAS has been more commonly seen in females. But in our study, only 2 out of the 14 RAS patients were females. However the association of gender an RAS is not significant (p=0.151).

HYPERTENSION AND RAS

Hypertension has long been established as a predisposing cause and a consequence of RAS. Hypertension was defined as blood pressure

>140/90 mmHg in our study. 11 out of the 14 RAS patients were hypertensives. Cohen et al study observed hypertension to be an independent risk factor for ARAS and the p value for the association of hypertension was found to be 0.011.[49] In the Buller et al study the systolic blood pressure was significantly associated with ARAS with a p value of 0.0001.[50] The diastolic blood pressure association with ARAS was not significant (p value-0.4483).

DIABETES MELLITUS AND RAS

Diabetes mellitus has been identified to be an independent risk factor for RAS previously reported studies including the Cohen e al and Buller et al study. Even our study demonsrates the associaion of diabetes mellitus and RAS but the associaion is not significant(p value-0.497).[49,50]

SERUM CHOLESTEROL AND RAS

Out of the 14 RAS patients, 12 patients had high cholesterol levels and hypercholesterolemia was observed to be significantly associated with RAS(p=0.005). In the Cohen et al and the Buller et al study, though hypercholesterolemia was observed to be a predictive factor, it was not significantly associated with RAS.[49,50]

CREATININE CLEARANCE AND RAS

The creatinine clearance in ml/min calculated by the Cockroft and Gault formula was found to be significantly associated with RAS (p=0.001).

The logistic regression of our study was obtained to be:

Probability(patient having RAS)=

1/(1+exp(-(-102.247+(0.655*Age)+(21.371*Serum Creatinine) + (0.354*Creatinine Clearance)+(6.022*Lipid Profile)+(3.927*Extent Of CAD)+(4.327*Hypertension)).

It was observed that if probability (patient having RAS) > 0.5, patients were at a more risk of having RAS.

Using the above regression equation we were able to classify, 98% of non-RAS patients (84 out of 85) and 80% of RAS patients (11 out of 14) correctly.

The Cohen et al study has established Nomogram to calculate the predictive score for significant RAS based on clinical profile of the patients.[49] It is as below:

CLINICAL PARAMETER	SCORE
AGE	
< 64 years	0
64-72 years	2
>73 years	4
FEMALE SEX	2
HYPERTENSION	2
NO. OF CARDIAC DRUGS	
None	0
1 drug	1
2 drugs	3
3drugs	4
PERIPHERAL VASCULAR DISEASE	4
PREVIOUS MULTIVESSEL DISEASE OR CABG	2
CREATININE (mg/dl)	
<0.8	0
0.8-0.99	1
1-1.19	3
1.2-1.39	4
1.4-1.59	6
1.6-1.79	7
1.8-1.99	9
2-2.19	10
>2.20	12

This score has enabled to stratify patients and determine the need for renal angiogram. Patients having a score of 11 or more are chosen for renal artery screening.

CONCLUSIONS

- The true clinical occurrence of RAS is more than that reported.
- Early identification of patients having RAS can help to early institution of treatment and hence prevention of long term complications and better prognosis.
- In our study, age> 60 years (p=0.001), creatinine clearance (p=0.001), lipid profile (p=0.002), serum creatinine (p=0.005), extent of CAD (p=0.0080) were observed to be significantly associated with ARAS at 0.01 level of significance.
- Male gender, hypertension, diabetes mellitus, smoking were observed to be other independent risk factors.
- The logistic regression was obtained to be:

  Probability (patient having RAS)=

  1/(1+exp(-(-102.247+(0.655*Age)+(21.371*Serum Creatinine) + (0.354*Creatinine Clearance)+(6.022*Lipid Profile) + (3.927* Extent Of CAD) + (4.327 * Hypertension)).

  It was observed that if probability (patient having RAS) > 0.5, patients were at a more risk of having RAS.

LIMITATIONS OF THE STUDY

- The impact of clinical identification of incidental RAS on the long term outcome of the patient has not been studied.

- Being done in a single centre there may be referral bias.

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PROFORMA

Name:

Age/ sex:

Educational status: **Occupation:**

Marital status:

Address:

Contact number:

CLINICAL FEATURES: DURATION

1) Difficulty in breathing
2) Chest pain
3) Syncope
4) Cough
5) Oliguria
6) Leg swelling
7) Facial puffiness
8) Fatiguability
9) Abdominal pain/ distension
10) Altered sensorium

PAST HISTORY:

IHD.....(duration.....; treatment.....)

Renal disease.....(duration.....; treatment.....)

Hypertension.....(duration.....; treatment.....)

Diabetes mellitus.....(duration.....; treatment.....)

Stroke.....(duration.....; treatment.....)

Other significant past history:

PERSONAL HISTORY:

Diet: vegetarian/ non- vegetarian/ mixed/ fruits/ fast food

Appetite- good/ poor

Bowel- normal/ constipation/ loose stools

Bladder- normal/ polyuria/ oliguria

Sleep- normal/ reduced

Mental stress- low/ mod/ high

Smoking- smoker

Ex- smoker (quit since.....)

Alcohol- duration- Unit-

Tobacco-

Exercise-

TREATMENT HISTORY:

FAMILY HISTORY:

Coronary artery disease

Hypertension

Diabetes mellitus

Stroke

Renal disease

GENERAL PHYSICAL EXAMINATION:

Pallor

Cyanosis

Clubbing

Icterus

Pedal edema

Lymphadenopathy

VITAL SIGNS:

Temperature (in F):

Pulse (/ min):

BP (mm of Hg):

Pulse pressure (mm of Hg):

Respiratory rate:

SYSTEMIC EXAMINATION:

CVS:

RS:

PA:

CNS:

INVESTIGATIONS:

ECG: ECHO:

CXR:

CBC:

TC- DC- Hb- ESR- Platelet-

BLOOD SUGAR:

RBS- FBS- PPBS-

LIPID PROFILE-

VLDL- LDL- HDL- Total

Cholesterol- TGL-

RENAL PARAMETERS-

Blood urea-

Serum creatinine-

Sr.Na- Sr.K- Sr.Cl- Sr. HCO3-

URINE-

Sugar- Protein-

Cells/ casts-

ULTRASOUND ABDOMEN-

CAG REPORT:

SITE(S):

EXTENT:

NUMBER OF VESSELS INVOLVED:

RENAL ANGIOGRAM REPORT:

SITE:

EXTENT:

UNILATERAL/ BILATERAL:

OTHER INVESTIGATIONS:

CONSENT FORM

(1) I agree to {permit my relative(mention relation)} participate in the study entitled, "**Prevalence and predictors of Renal artery stenosis (RAS) in coronary artery disease (CAD) patients undergoing Coronary angiogram (CAG) in Government Stanley Hospital, Chennai".**

(2) I confirm that i have been told about this study to be conducted on my relative in my mother tongue and have had the opportunity to ask questions.

(3) I understand that the participation is voluntary and we may refuse to participate at any time without giving reasons and without affecting my benefits.

(4) I agree not to restrict the use of any data or results that may arise from this study.

Name of the participant: Sign/ thumbprint:

Name of the relative: Sign/ thumbprint:

Relationship:

Sign of the investigator:

நோயாளிகளுக்கான தகவல் படிவம்

எனக்கு இருதய இரத்த குழாய் அடைப்பு உள்ளதா என்பதை கண்டறிய இருதய உட்புகுத்து பரிசோதனையும், கொரோனரி ஏஜ்ஜியோகிராமும் செய்ய வேண்டியதன் அவசியம் மருத்துவரால் விளக்கப்பட்டது. அவ்வாறு இருதய இரத்த குழாய் பரிசோதனை செய்யும் பொழுது, ஆராய்ச்சி நோக்கத்திற்காக ரீனல் ஏஜ்ஜியோகிராம் செய்து, சிறுநீரக இரத்த குழாயினையும் பரிசோதனை செய்து கொள்வதன் பயனை மருத்துவரின் விளக்கத்தினால் அறிந்தேன். இதனால் ஏற்படக்கூடிய மிக அரிதான பக்க விளைவுகள் மருத்துவரின் மூலம் தெரிவிக்கப்பட்டது.

நான் இப்பரிசோதனையின் முடிவுகளை வைத்து இந்த ஆய்வினை மேற்கொள்ள சம்மதம் அளிக்கிறேன். மேலும் என் வியாதிக்கு தேவையான பரிசோதனைகள் மட்டுமே செய்யப்படும் என்றும், தேவையற்ற பரிசோதனைகள் எதுவும் மேற்கொள்ளப்படாது என்றும் மருத்துவரின் மூலம் அறிந்துக் கொண்டேன். இப்படிவத்தை முழுவதும் படித்துப் பார்த்து இந்த ஆய்விற்கு முழுமனதுடன் சம்மதம் தெரிவித்து கீழே கையொப்பம் அளிக்கிறேன்.

இடம் :

நாள் :

நோயாளி/உறவினரின் கையொப்பம்

இடது பெருவிரல் ரேகை

(மருத்துவரால் படித்துக்காட்டப்பட்டது)

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு

"இருதய இரத்த குழாய் அடைப்பிற்காக கொரோனரி ஏஞ்ஜியோகிராம் செய்யப்படும் நோயாளிகளில், சிறுநீரக இரத்த குழாய் அடைப்பினை கண்டறியும் ஆய்வு"

ஆராய்ச்சி நிலையம் : அரசு ஸ்டான்லி மருத்துவமனை
சென்னை - 600 001.

பங்கு பெறும் நோயாளியின் பெயர் : வயது :

பங்கு பெறும் நோயாளியின் எண் : பாலினம் : ஆண் ☐ பெண் ☐

நோயாளியின் விலாசம் :

நோயாளி இதனை (✓) குறிக்கவும்.

மேலே குறிப்பிடப்பட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும். அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் என்னை இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்க அனுமதிக்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் என்னை இவ்வாய்வில் இருந்து விலக்கி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். என்னை ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக் கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்த கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன். என் உடல் பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கத்திற்கு மாறான நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்துவ அணிக்கு தெரிவிப்பேன் என உறுதி அளிக்கிறேன். ☐

நோயாளியின் கையொப்பம் ..... இடம் ..... தேதி

கட்டைவிரல் ரேகை (இந்த படிவம் படித்து காட்டப்பட்டு புரிந்து கைரேகை அளிக்கின்றேன்)

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

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ஆய்வாளரின் கையொப்பம் ..... இடம் ..... தேதி

ஆய்வாளரின் பெயர் .....

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Prevalence and predictors of renal artery stenosis (RAS) In coronary artery disease (CAD) patients undergoing Coronary angiogram (CAG) in Govt.Stanley Hospital,

Principal Investigator : Dr.J.Arokia Philo Aarthy

Designation : PG in M.D(Gen.Med)

Department : Department of General Medicine
Government Stanley Medical College,
Chennai-1

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 11.06.2012 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

Sr. No	Age	Weight	Sex	Hypertension	Diabetes mellitus	Sr. creatinine	Estimate creatinine clearance (ml/min)	Lipid profile	Smoking	Family History	RAS	UL/BL	Site of RAS	Extent of CAD (no. of vessels)
1	54	65	1	1	0	0.9	86.3	1	1	1	0			1
2	50	68	1	1	1	1	85	0	0	0	0			2
3	52	70	0	1	1	0.8	69.5	0	1	0	0			0
4	65	74	1	1	0	1	86.3	1	1	0	1	0	proximal	0
5	58	76	0	1	1	1	73.6	0	1	0	0			1
6	55	60	1	1	0	0.9	78.7	0	0	0	0			0
7	56	63	1	0	1	0.8	91.9	1	1	1	0			1
8	55	70	0	1	0	1	70.2	0	1	0	0			0
9	64	72	1	0	1	1.1	69.1	0	1	0	0			0
10	68	70	1	1	1	1.1	72.5	1	1	0	1	1	proximal	0
11	59	66	1	1	1	0.8	92.8	1	1	0	0			0
12	68	67	0	1	0	0.9	63.3	1	1	1	0			1
13	69	72	1	0	1	0.9	78.9	1	0	0	0			0
14	55	70	0	1	0	1.1	63.9	0	0	0	0			2
15	66	60	1	1	0	0.8	77.1	1	1	0	0			0
16	60	64	1	1	1	0.8	88.9	1	1	1	0			1
17	59	68	0	1	1	1	65	0	0	0	0			0
18	58	65	1	1	1	0.9	82.3	1	1	0	0			0
19	62	72	1	0	1	0.8	112.5	1	1	1	1	0	branch	0
20	56	80	0	1	0	0.9	88.1	1	1	0	0			1
21	55	81	1	1	1	1	95.6	0	0	1	0			0
22	49	68	0	1	1	1.1	68.1	0	1	0	0			1
23	48	60	1	0	0	0.7	109.5	0	1	0	0			0
24	60	62	1	1	0	0.9	76.5	1	1	0	0			2
25	62	72	0	1	1	1	66.3	1	0	1	0			2
26	49	82	1	1	1	1.1	95.3	0	1	1	0			0
27	56	79	0	1	0	1.1	71.2	1	1	1	0			0
28	58	80	1	0	1	1.2	75.9	0	0	1	0			0
29	44	69	1	1	1	0.9	102.2	1	1	0	0			2
30	48	70	0	0	1	0.8	95	0	1	0	0			0
31	65	74	0	1	0	1	72.5	1	1	0	1	1	branch	1
32	65	75	1	1	1	0.9	78.4	1	0	1	0			0
33	63	88	1	1	1	1.2	78.4	0	1	1	0			0
34	62	69	0	0	1	1	63.5	1	1	0	0			1
35	64	73	1	1	0	1	77.1	0	1	0	0			0
36	55	72	0	1	0	0.9	73.3	1	1	1	0			0
37	57	70	1	0	0	0.8	100.9	0	0	1	0			0
38	50	66	0	1	1	1	82.5	1	1	1	0			1
39	62	76	1	1	1	1	76.3	1	1	1	1	0	proximal	1
40	60	69	1	1	1	0.9	85.2	1	1	0	0			0
41	58	60	0	1	1	0.9	64.5	0	0	0	0			1
42	55	72	1	0	0	1	85	1	1	1	0			0
43	56	66	0	1	0	0.9	85.6	0	1	1	0			0
44	49	74	1	1	0	0.8	116.9	1	1	0	0			0
45	68	78	1	0	1	1	106.2	0	1	0	1	1	branch	1
46	67	60	1	1	1	0.8	76	0	0	1	0			1

47	68	79	1	1	0	1.1	83.8	0	1	1	0			0
48	62	66	0	0	1	1	71.5	0	1	0	0			0
49	63	77	1	1	1	1.1	74.9	0	1	1	0			1
50	63	78	1	1	1	0.9	91.7	1	1	1	1	0	mid	0
51	65	63	1	1	1	0.8	91.9	1	1	0	1	1	mid	0
52	66	65	1	1	1	0.7	95.4	1	0	0	0			0
53	65	72	1	1	1	0.9	83.3	0	1	1	0			1
54	68	72	0	1	0	0.9	68	0	1	1	0			2
55	70	79	1	1	0	1	76.8	0	0	0	0			0
56	67	72	1	0	1	0.8	92.1	1	1	1	1	0	mid	0
57	67	76	1	1	1	1	77.1	0	0	1	0			1
58	64	76	0	1	1	1	68.2	0	1	1	0			0
59	60	69	1	1	1	0.9	85.2	1	1	0	0			0
60	57	71	1	1	0	1.1	74.4	0	0	0	0			2
61	56	75	1	0	1	0.9	97.2	1	1	1	0			0
62	47	69	0	1	1	0.9	84.2	0	1	1	0			1
63	48	77	1	1	0	1.1	89.4	1	1	1	0			0
64	50	66	1	1	1	1	82.5	0	1	1	0			0
65	66	74	1	1	1	0.8	82.2	1	0	0	1	0	proximal	0
66	52	60	0	1	1	0.8	77.9	0	1	0	0			0
67	55	62	1	0	1	0.8	91.5	1	1	0	0			0
68	57	81	1	1	1	0.9	103.8	0	0	0	0			0
69	58	80	0	1	0	1.2	64.5	0	1	0	0			0
70	59	68	1	1	1	1.1	69.5	1	1	1	0			0
71	60	69	1	1	1	0.9	85.2	1	1	0	1	0	proximal	0
72	65	72	1	1	1	1.1	68.2	1	0	0	0			0
73	69	70	0	1	1	1.1	53.3	1	1	0	0			1
74	63	66	1	0	0	1	70.6	0	0	1	0			0
75	58	62	1	0	0	1	70.6	1	1	0	0			0
76	53	63	0	1	0	0.9	71.9	0	1	0	0			1
77	52	64	1	1	1	0.8	97.8	0	1	0	0			0
78	51	70	1	1	1	1.1	78.7	1	0	1	0			0
79	56	72	0	0	0	1.2	59.5	0	0	0	0			2
80	54	82	1	1	0	1.2	81.6	1	1	0	0			0
81	55	84	0	0	1	1.2	82.6	0	1	0	0			0
82	68	68	1	0	1	0.9	75.6	1	1	0	0			1
83	67	69	0	1	0	0.9	74.2	1	1	1	1	0	proximal	0
84	63	70	1	1	1	1	74.9	0	0	0	0			0
85	62	76	1	0	1	1	82.3	1	1	0	0			0
86	63	70	0	0	1	1.1	57.8	0	0	0	0			0
87	59	80	1	1	0	1.2	75	0	0	0	0			0
88	58	84	1	1	0	1.2	79.7	0	0	0	0			0
89	42	60	1	0	0	0.9	90.7	1	1	1	0			2
90	68	70	0	1	1	1.2	49.6	1	1	0	0			0
91	61	82	1	1	1	1.2	75	0	1	0	1	0	proximal	0
92	66	69	1	1	1	1.1	64.5	0	0	0	0			0
93	46	63	1	1	0	0.9	91.4	1	0	0	0			2
94	48	67	1	0	0	0.9	95.1	0	0	0	0			0

95	64	72	0	0	1	1	64.6	1	1	0	0			0
96	62	76	1	1	1	1.2	68.6	1	1	1	1	0	proximal	0
97	62	78	1	1	1	1.2	70.4	1	1	0	0			0
98	56	80	0	1	0	1.2	77.8	0	0	0	0			1
99	54	69	0	0	1	0.9	77.8	1	0	1	0			2
100	64	72	0	0	1	1	64.6	1		0	0			0
	Age in yrs	Wt. in kg	1 - Male 0 - Female	E - Hypertension 1 - Present 0 - Absent	Diabetes Mellitus 1 - Present 0 - Absent	Serum creatinine (mg%)	Creatinine clearance (ml/minute) Cockroft Gault formula	Serum Cholesterol 1 - High 0 - Normal	Smoking 1 - Present 0 - Absent	Family History 1 - Present 0 - Absent	RAS 1 - Present 0 - Absent	Location of RAS 1 - Bilateral 0 - Unilateral	Site of RAS 1 - Bilateral 0 - Unilateral	Extent of CAD 0 - Multivessel 1 - Single vessel 2 - No significant CAD